

100

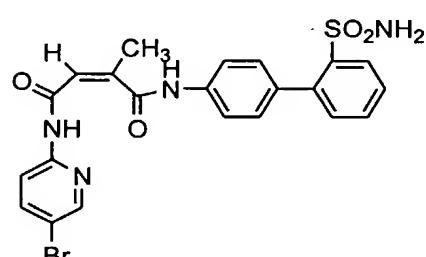
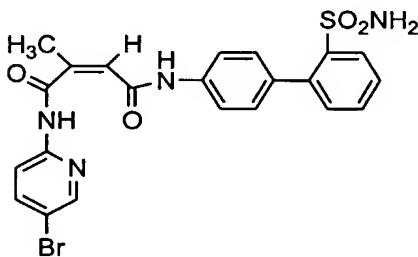
B. Preparation of N-(4-bromophenyl)-N<sup>4</sup>-(4-[(2-aminosulfonyl)phenyl]phenyl)-maleamic amide.

To a solution of 4-bromoaniline (93 mg, 0.543 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) at room temperature, trimethylaluminum (0.82 mL, 2.0 M in hexane, 1.64 mmol) was added dropwise. After the solution was stirred for 30 min at room temperature, compound N-(4-[(2-tert-butylaminosulfonyl)phenyl] phenyl)maleamic methyl ester (113 mg, 0.272 mmol) was added. The mixture was stirred at room temperature for 2 days. The solution was neutralized with 1N HCl to pH 2-3. Water and CH<sub>2</sub>Cl<sub>2</sub> were added, and organic phase was separated, dried over Na<sub>2</sub>SO<sub>4</sub>, concentrated in vacuo. The residue was dissolved in TFA (4 mL). It was allowed to stand at room temperature overnight. TFA was removed in vacuo. The residue was purified by HPLC using a gradient of 5% CH<sub>3</sub>CN in H<sub>2</sub>O (containing 0.1% TFA) to 95% CH<sub>3</sub>CN over 60 min. Fractions containing the desired product were pooled, and lyophilized to give a powder (8 mg, yield: 6%). MS 500 and 502 (M + H), 522 and 524 (M + Na). <sup>1</sup>H NMR (CD<sub>3</sub>OD) 8.09 (d, 1H, J = 8 Hz), 7.68 (d, 2H, J = 8 Hz), 7.64 – 7.28 (m, 9H), 6.45 (AB type, 2H).

Examples 44 and 45

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**Preparation of N<sup>1</sup>-(5-bromopyridin-2-yl)-N<sup>4</sup>-(4-[(2-aminosulfonyl)phenyl]phenyl)-2-methylmaleamic amide and N<sup>1</sup>-(5-bromopyridin-2-yl)-N<sup>4</sup>-(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.**



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A. Preparation of N-(5-bromopyridin-2-yl)-methylmaleimide.

A mixture of citraconic anhydride (1.00 mL, 11.1 mmol) and 2-amino-5-bromopyridine (1.93 g, 11.2 mmol) in toluene (60 mL) was heated to reflux overnight.

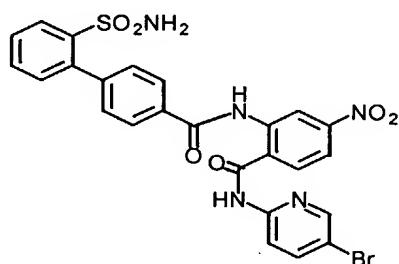
The solution was cooled down, filtered. The filtrate was concentrated in vacuo to give a solid (2.10 g, yield: 71%). MS 267 and 269 ( $M + H$ ).

B. Preparation of  $N^1$ -(5-bromopyridin-2-yl)- $N^4$ -(4-[(2-aminosulfonyl)phenyl] phenyl)-2-methylmaleamic amide and  $N^1$ -(5-bromopyridin-2-yl)- $N^4$ -(4-[(2-aminosulfonyl)phenyl]phenyl)-3-methylmaleamic amide.

To the solution of 4-(2-aminosulfonylphenyl)aniline (0.170 g, 0.685 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) at room temperature, trimethylaluminum (2.0 M in hexane, 2.00 mL, 4.00 mmol) was added dropwise, during which time, white gel-like precipitates came out the solution. It was stirred for 30 min. A solution of N-(5-bromopyridin-2-yl)-methylmaleimide (0.122 g, 0.457 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) was added. It was stirred for 1 hour, during which time the precipitates started to dissolve, and the solution became clear. It was stirred for another 2 hours. 1N HCl was added to neutralize the solution to pH 2-3, which resulted in precipitation. The precipitates were collected by filtration, dried on vacuum. The precipitates (75 mg, yield: 32%) were a mixture of 2-methyl and 3-methylmaleamic amide isomers in a ratio of 1 : 5. MS 515 and 517 ( $M + H$ ), 537 and 539 ( $M + Na$ ).

20    Example 46

**N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-nitrophenylcarboxamide.**



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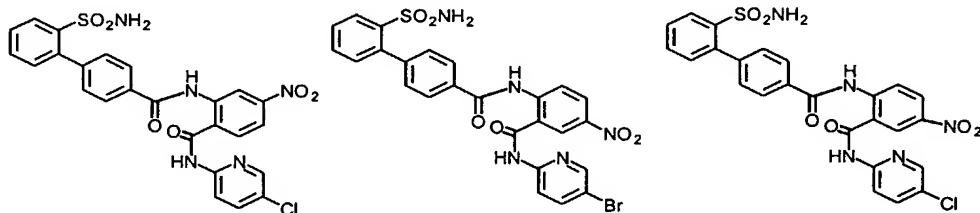
Step 1: A solution of 2-amino-4-nitrobenzoic acid (182 mg, 1 mmol, 1 equiv) in 10 mL of methanol was treated with thionyl chloride in portions until complete reaction. The solvent was evaporated and the residue was dissolved in 10 mL of pyridine. To the solution were added 4-[(2-t-butylaminosulfonyl)phenyl]benzoic acid (330 mg, 1

equiv) and  $\text{POCl}_3$  (0.93 mL, 10 equiv). The resulting mixture was stirred at rt overnight, quenched by slow addition of water, and extracted with  $\text{EtOAc}$ . The organic layer was dried over  $\text{MgSO}_4$ , filtered and flash chromatographed to give methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)amino-4-nitrobenzoate (430 mg, 84%). MS found for  $\text{C}_{25}\text{H}_{26}\text{N}_3\text{O}_7\text{S} (\text{M}+\text{H})^+$ : 512.

Step 2: To A solution of 2-amino-5-bromopridine (135 mg, 4.0 equiv) in 5 mL of methylene chloride treated with  $\text{AlMe}_3$  (2M in hexane, 1 mL, 10 equiv) for 30 min was added methyl 2-(4-[(2-t-butylaminosulfonyl)phenyl]phenylcarbonyl)amino-4-nitrobenzoate (100 mg, 0.2 mmol, 1 equiv). The mixture was stirred at rt overnight, quenched with saturated aqueous potassium sodium tartrate. The organic layer was dried over  $\text{MgSO}_4$ , filtered, evaporated and refluxed in 2 mL of trifluoroacetic acid for 30 min. TFA was then evaporated and HPLC (C18 reversed phase) eluting with 0.5% TFA in  $\text{H}_2\text{O}/\text{CH}_3\text{CN}$  gave N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-nitrophenylcarboxamide (42 mg, 36%). MS found for  $\text{C}_{25}\text{H}_{19}\text{BrN}_5\text{O}_6\text{S} (\text{M}+\text{H})^+$ : 596.

#### Examples 47-49

The following compounds of Examples 47-49 were prepared according to the procedure described in example 46.



Example 47

MS ( $\text{M}+\text{H})$ :  
552

Example 48

MS ( $\text{M}+\text{H})$ :  
596

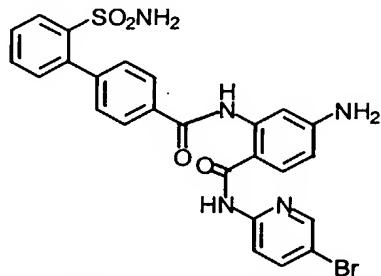
Example 49

MS ( $\text{M}+\text{H})$ :  
552

Example 50

**N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide.**

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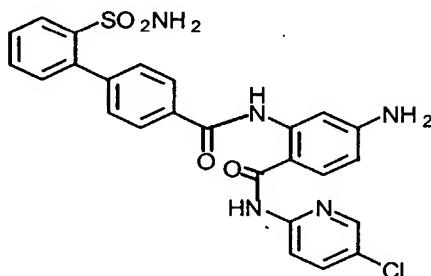


A solution of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-nitrophenylcarboxamide (65 mg, 0.1 mmol, 1 equiv) in 10 mL of EtOAc was treated with SnCl<sub>2</sub>·2H<sub>2</sub>O (90 m g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, 10 washed with saturated aqueous NaHCO<sub>3</sub> and 1N NaOH. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-aminophenyl carboxamide, which was refluxed with 2 mL of TFA for 1h. After removal of TFA by rotavap, the residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN 15 to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide (47 mg, 84%). MS found for C<sub>25</sub>H<sub>21</sub>BrN<sub>5</sub>O<sub>4</sub>S (M+H)<sup>+</sup>: 566.

Example 51

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**N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-aminophenylcarboxamide.**

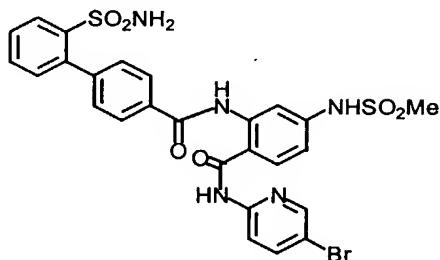


This compound was prepared according to the procedure described in example 50. MS found for  $C_{25}H_{21}ClN_5O_4S$  ( $M+H$ ) $^+$ : 522.

Example 52

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**N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide.**



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A solution of N-(5-bromo-2-pyridinyl)-(2-(4-[(2-t-butylsulfonyl)phenyl]phenylcarbonyl) amino)-4-aminophenyl carboxamide (62 mg, 0.1mmol, 1 equiv) in 3 mL of  $CH_2Cl_2$  was treated with  $MsCl$  (23 mg, 2 equiv) and TEA (0.5 mL) at rt for 4 h. The mixture was washed with water and dried over

15

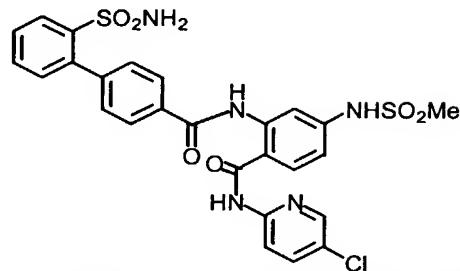
$MgSO_4$ , filtered and evaporated. The residue was refluxed with 2 mL of TFA for 1h. After removal of TFA by rotavap, the residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in  $H_2O/CH_3CN$  to give N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide (33 mg, 52%). MS found for

20

$C_{26}H_{23}BrN_5O_6S2$  ( $M+H$ ) $^+$ : 644.

Example 53

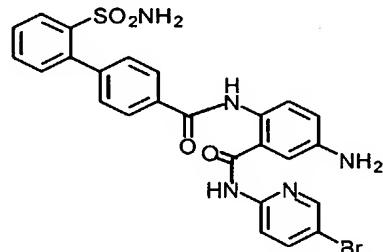
5    **N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-4-methylsulfonylaminophenylcarboxamide.**



This compound was prepared according to the procedure described in example 53. MS found for  $C_{26}H_{23}ClN_5O_6S_2$  ( $M+H$ )<sup>+</sup>: 600.

10    Example 54

**N-(5-bromo-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide.**



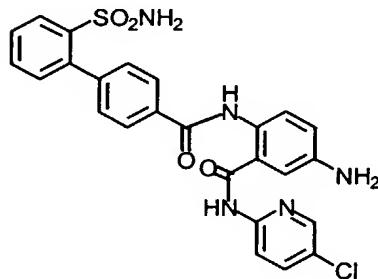
15

This compound was prepared according to the procedure described in example 50. MS found for  $C_{25}H_{21}BrN_5O_4S$  ( $M+H$ )<sup>+</sup>: 566.

Example 55

**N-(5-chloro-2-pyridinyl)-(2-(4-[(2-aminosulfonyl)phenyl]phenylcarbonyl)amino)-5-aminophenylcarboxamide.**

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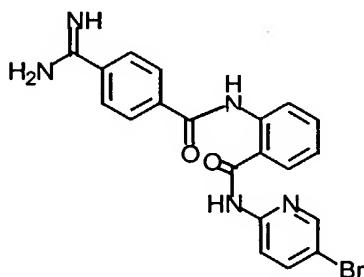
This compound was prepared according to the procedure described in example 50. MS found for  $C_{25}H_{21}ClN_5O_4S$  ( $M+H$ ) $^+$ : 522.

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Example 56

**N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)-phenylcarboxamide.**

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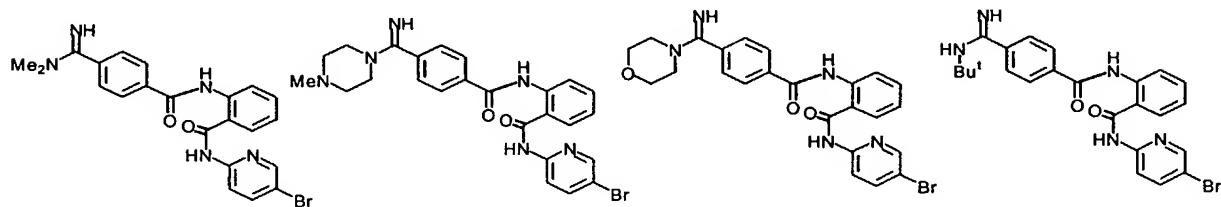


Step 1: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)phenylcarboxamide (292 mg, 1 mmol, 1.0 equiv), 4-cyano benzoyl chloride (165 mg, 1 equiv), pyridine (3 mL) in 10 mL of dichloromethane was stirred at rt overnight, washed with H<sub>2</sub>O. The organic layer was dried over MgSO<sub>4</sub>, filtered, evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (349 mg, 70%). MS found for  $C_{20}H_{14}BrN_4O_2$  ( $M+H$ ) $^+$ : 421.

Step 2: A stream of HCl(g) was bubbled through a 0°C solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and 5 evaporated. The resulting residue was treated with ammonium acetate (40 mg) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN to give N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)-phenylcarboxamide (31 mg, 70%). MS found for 10 C<sub>20</sub>H<sub>17</sub>BrN<sub>5</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 438.

#### Examples 57-86

The following compounds of Examples 57-86 were prepared according to the 15 procedure described in example 56.



Example 57

MS (M+H):  
466

Example 58

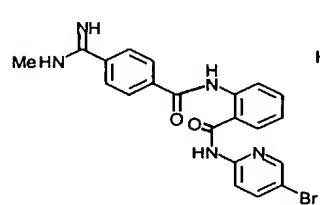
MS (M+H):  
521

Example 59

MS (M+H):  
508

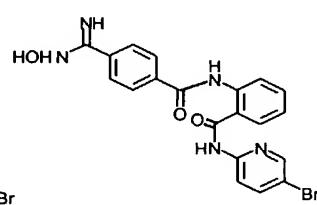
Example 60

MS (M+H):  
494



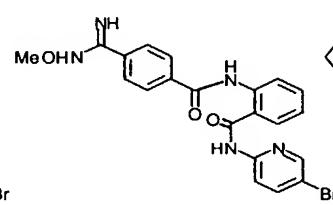
Example 61

MS (M+H):  
452



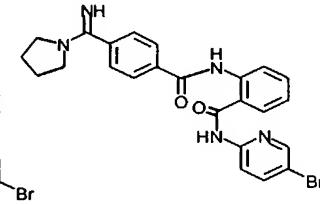
Example 62

MS (M+H):  
454



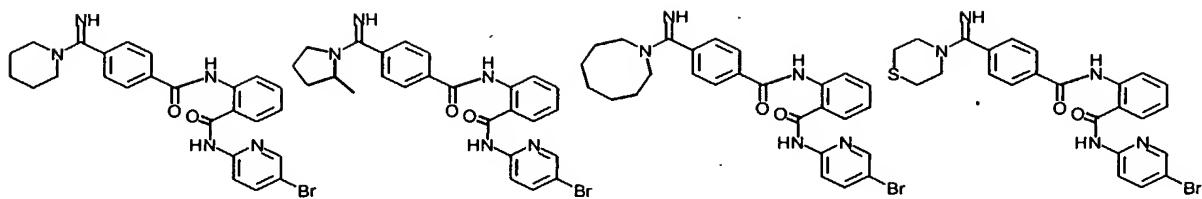
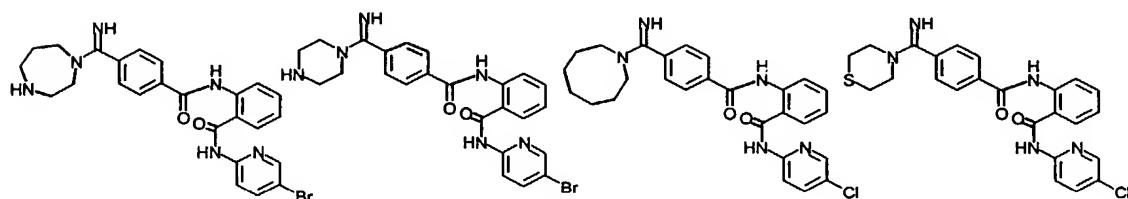
Example 63

MS (M+H):  
468

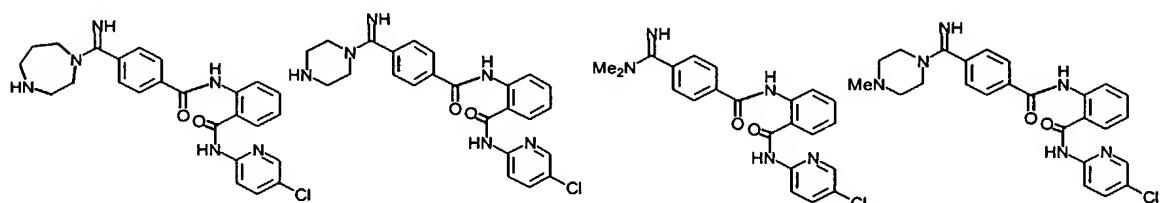


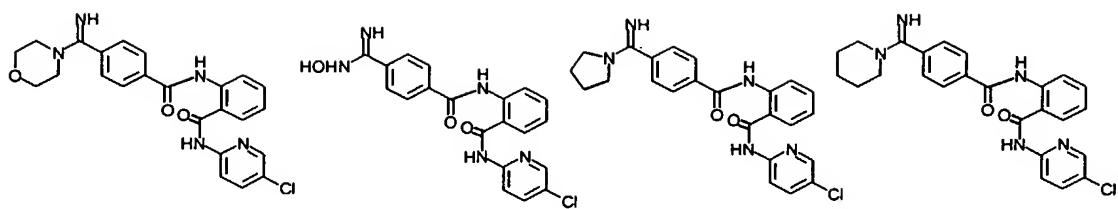
Example 64

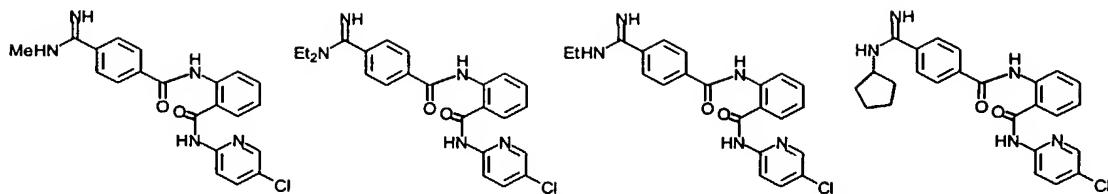
MS (M+H):  
492

Example 65MS (M+H):  
506Example 66MS (M+H):  
506Example 67MS (M+H):  
520Example 68MS (M+H):  
524Example 69MS (M+H):  
521Example 70MS (M+H):  
507Example 71MS (M+H):  
476Example 72MS (M+H):  
480

5

Example 73MS (M+H):  
477Example 74MS (M+H):  
463Example 75MS (M+H):  
422Example 76MS (M+H):  
477

Example 77MS (M+H):  
464Example 78MS (M+H):  
410Example 79MS (M+H):  
448Example 80MS (M+H):  
462

Example 81

MS (M+H): 408

Example 82

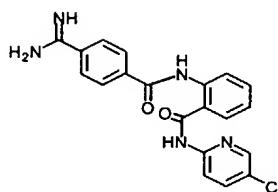
MS (M+H): 22

Example 83

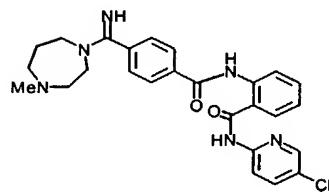
MS (M+H): 450

Example 84

MS (M+H): 462

Example 85

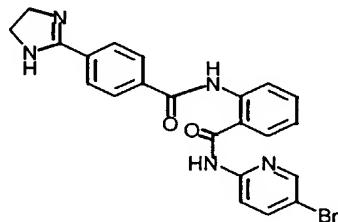
MS (M+H): 394

Example 86

MS (M+H): 491

5    Example 87

**N-(5-bromo-2-pyridinyl)-(2-(4-(2-imidazolinyl)phenylcarbonyl)amino)-phenylcarboxamide.**



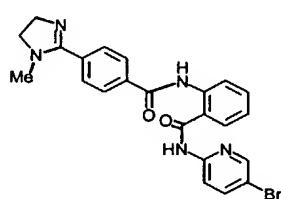
10

A stream of HCl(g) was bubbled through a 0°C solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) in 5 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. The

resulting residue was treated with ethylene diamine (40 mg) in 10 ml methanol at reflux temperature for 2 h. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(2-imidazolinyl)phenylcarbonyl)amino)-phenylcarboxamide (41 mg, 89%). MS found for C<sub>22</sub>H<sub>19</sub>BrN<sub>5</sub>O<sub>2</sub>(M+H)<sup>+</sup>: 464.

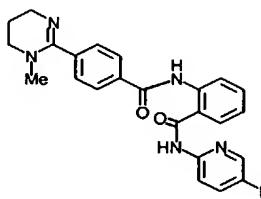
### Examples 88-96

10 The following compounds of Examples 88-96 were prepared according to the procedure described in example 87.



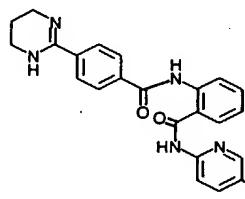
Example 88

MS (M+H): 478



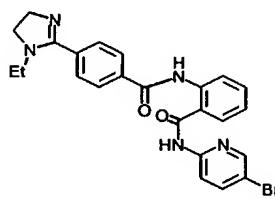
Example 89

MS (M+H): 492



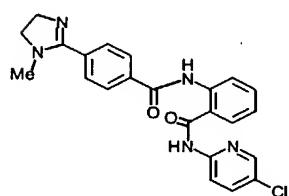
Example 90

MS (M+H): 478



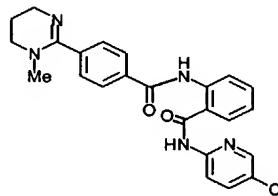
Example 91

MS (M+H): 492



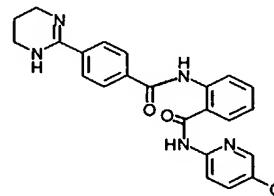
Example 92

MS (M+H): 434



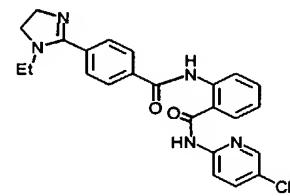
Example 93

MS (M+H): 448



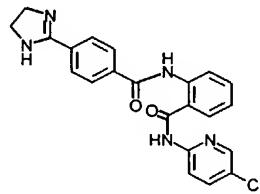
Example 94

MS (M+H): 434



Example 95

MS (M+H): 448

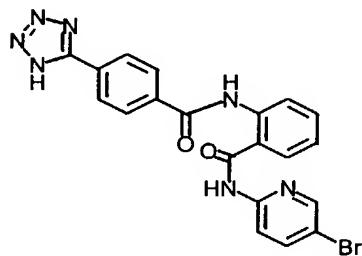


Example 96

MS (M+H): 420

Example 97

5      **N-(5-bromo-2-pyridinyl)-(2-(4-(5-tetrazolyl)phenylcarbonyl)amino)-phenylcarboxamide.**

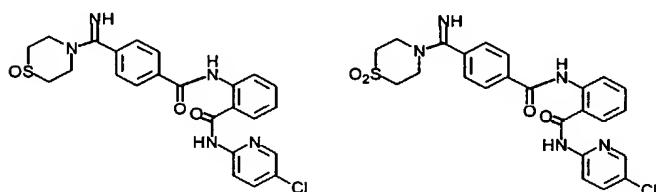


10     A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)-phenylcarboxamide (49 mg, 0.1 mmol) and sodium azide (67 mg, 10 equiv) in 5 mL of DMF was heated at 100°C for 24h. The reaction mixture was diluted with EtOAc, washed with water, dried, filtered and evaporated. The residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(5-tetrazolyl)phenylcarbonyl)amino)-phenylcarboxamide (33 mg, 65%). MS found for C<sub>20</sub>H<sub>15</sub>BrN<sub>7</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 464.

15

Example 98 and Example 99

20     **N-(5-bromo-2-pyridinyl)-(2-(4-[1,1-doxo(1,4-thiazaperhydroin-4-yl)iminimethyl]phenylcarbonyl)amino)-phenylcarboxamide and N-(5-bromo-2-pyridinyl)-(2-(4-[1-oxo(1,4-thiazaperhydroin-4-yl)iminimethyl]phenylcarbonyl)amino)-phenylcarboxamide.**



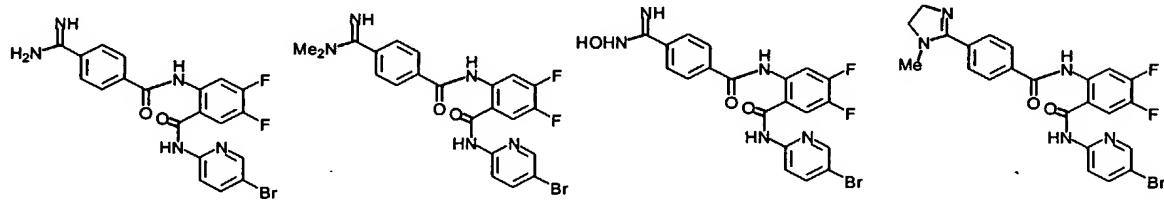
A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-(1,4-thiazaperhydroin-4-yl)iminimethyl)phenylcarbonyl)amino)-phenylcarboxamide (48 mg, 0.1 mmol) and 3 mL of 30% hydrogen dioxide was stirred at rt for 12h. The reaction was quenched with solid Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>. Purification by HPLC (C18 reversed phase) eluting with 0.5% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN gave N-(5-bromo-2-pyridinyl)-(2-(4-[1,1-doxo(1,4-thiazaperhydroin-4-yl)]iminimethyl)phenylcarbonyl)amino)-phenylcarboxamide (15 mg, 31%), MS found for C<sub>24</sub>H<sub>23</sub>ClN<sub>5</sub>O<sub>4</sub>S (M+H)<sup>+</sup>: 512 and N-(5-bromo-2-pyridinyl)-(2-(4-[1-oxo(1,4-thiazaperhydroin-4-yl)]iminimethyl)phenylcarbonyl)amino)-phenylcarboxamide (20 mg, 41%). MS found for C<sub>24</sub>H<sub>23</sub>ClN<sub>5</sub>O<sub>3</sub>S (M+H)<sup>+</sup>: 496.

10

Examples 100-105

The following compounds were prepared according to the procedure described in example 56 and example 87.

15

Example 100

MS (M+H): 474

Example 101

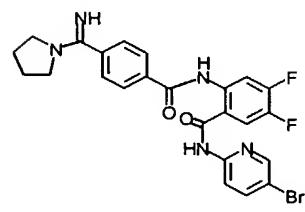
MS (M+H): 502

Example 102

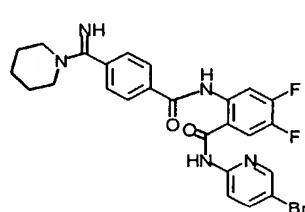
MS (M+H): 490

Example 103

MS (M+H): 514

Example 104

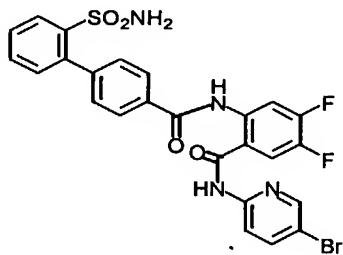
MS (M+H): 528

Example 105

MS (M+H): 542

Example 106

5    **N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)-4,5-difluorophenylcarboxamide.**



This compound is prepared according to the procedure described in example 27. MS found for C<sub>25</sub>H<sub>18</sub>BrF<sub>2</sub>N<sub>4</sub>O<sub>4</sub>S (M+H)<sup>+</sup>: 587.

10

Example 107

15    **3-(2-[(2-aminosulfonyl)phenyl]-2-fluorophenylaminocarbonyl-4-aminophenoxy) benzimidine.**

15

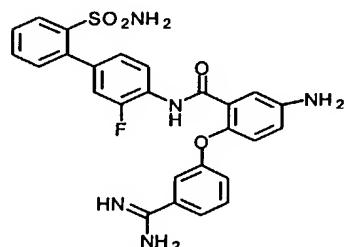


This compound is prepared according to the procedure described in example 17. MS found for C<sub>26</sub>H<sub>21</sub>FN<sub>5</sub>O<sub>6</sub>S (M+H)<sup>+</sup>: 550.

20

Example 108

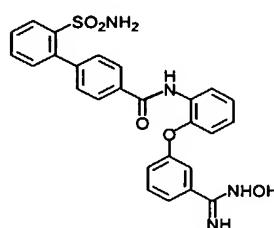
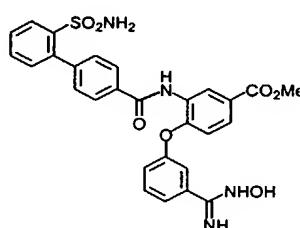
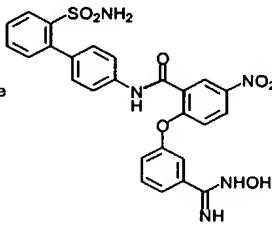
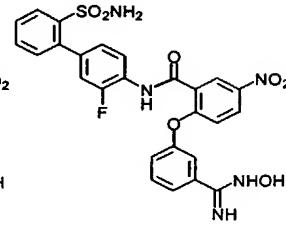
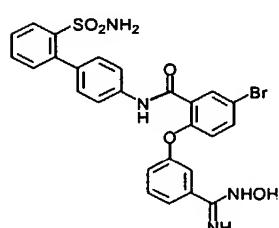
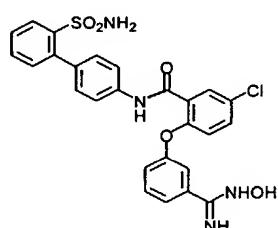
**3-(2-(4-[(2-aminosulfonyl)phenyl]phenylamino)phenyl)-2-fluorophenylaminocarbonyl-4-aminophenoxy benzimidine.**



5 This compound is prepared according to the procedure described in example 18. MS found for  $C_{26}H_{23}FN_5O_4S$  ( $M+H$ )<sup>+</sup>: 520.

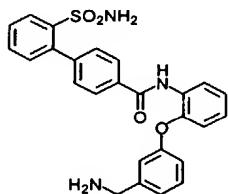
Examples 109-114

10 The following compounds were prepared according to the procedure described in example 1 except that in step 4,  $NH_2OH$  was used instead of  $NH_4OAc$ .

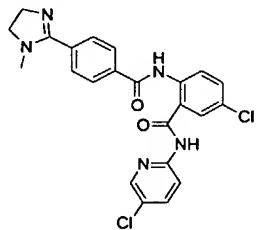
Example 109MS ( $M+H$ ): 502Example 110MS ( $M+H$ ): 560Example 111MS ( $M+H$ ): 547Example 112MS ( $M+H$ ): 547Example 113MS ( $M+H$ ): 581Example 114MS ( $M+H$ ): 537

Example 115

**3-(2-(4-[(2-amino sulfonyl)phenyl]benzoylamino) phenoxy)benzylamine.**



5 A mixture of 3-(2-(4-[(2-t-butylaminosulfonyl)phenyl]benzoylamino)phenoxy)benzonitrile (53 mg, 0.1 mmol) (53 mg, 0.1 mmol, 1 equiv), 5 mg of Pd/C (10%) in 10 mL of methanol was stirred at rt under 1 atm H<sub>2</sub> atmosphere overnight. After filtration through a thin layer of Celite and removal of the volatile, residue was refluxed in 2 mL of TFA for 1h, and purified  
10 by HPLC (C18 reversed phase) eluting with 0.5% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN to 3-(2-(4-(2-amino sulfonyl)phenyl)benzoylamino) phenoxy)benzylamine (13 mg, 27%). MS found for C<sub>26</sub>H<sub>24</sub>N<sub>3</sub>O<sub>4</sub>S (M+H)<sup>+</sup>: 474.

Example 116

15 Step 1: To a solution of 2-amino-5-chloropyridine (328mg, 2.55mmol) in tetrahydrofuran (5ml) was 0.5M potassium bis(trimethylsilyl)amide in toluene (10ml, 5.05mmol) dropwise at -78 °C. After stirred for additional 0.5hr at -78 °C, the mixture was added 5-chloroisatoic anhydride (0.5g, 2.55mmol) at -78 °C. The mixture was warmed up to r.t gradually and stirred overnight. After quenched by saturated ammonium chloride solution, the mixture was extracted by ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.71g, 100%). MS found for C<sub>12</sub>H<sub>9</sub>Cl<sub>2</sub>N<sub>3</sub>O M<sup>+</sup>=282, (M+2)<sup>+</sup>=284.

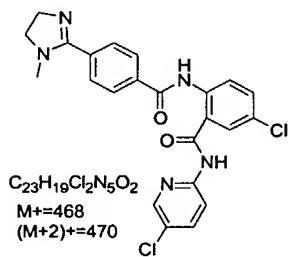
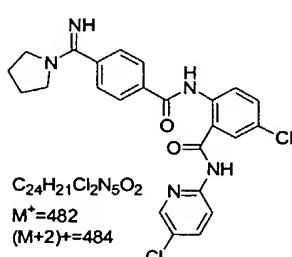
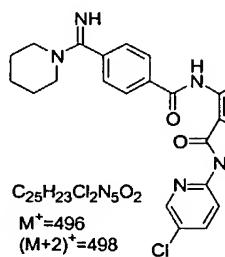
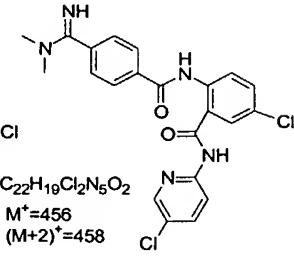
Step 2: To a solution of the compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.71g, 2.52mmol) in dichloromethane (10ml) was added 3-cyanobenzoyl chloride (417mg, 2.52mmol) and pyridine (0.611ml, 7.55mmol). The mixture was stirred at r.t. overnight. The precipitate was filtered and washed with dichloromethane to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide as a solid (683mg, 66%).  
 MS found for C<sub>20</sub>H<sub>12</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>2</sub> M<sup>+</sup>=411, (M+2)<sup>+</sup>=413.

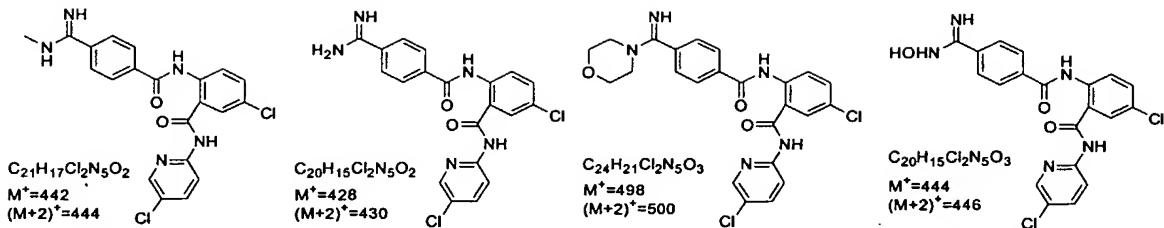
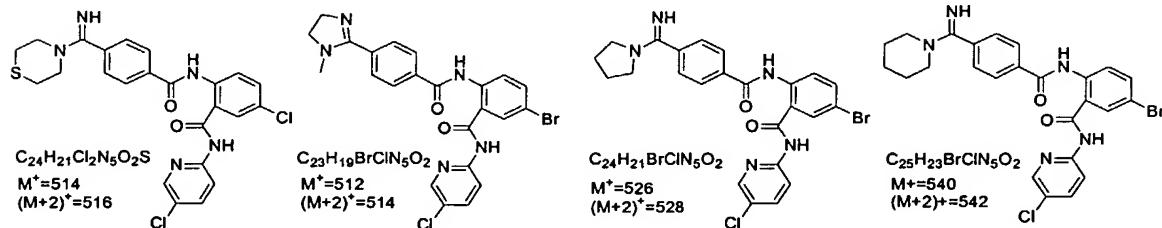
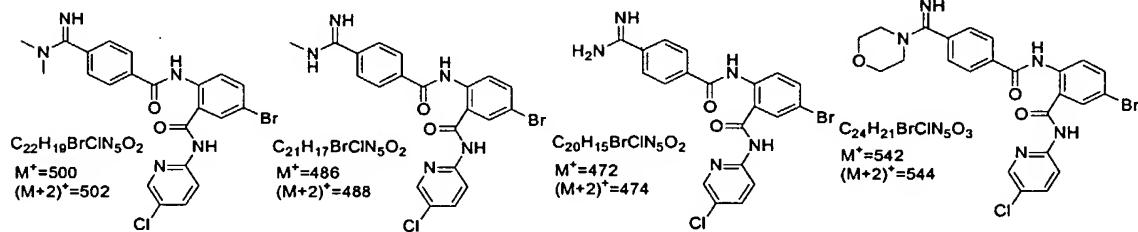
Step 3: To a solution of the compound of N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide (683mg, 1.66mmol) in anhydrous pyridine (10ml) and triethyl amine (1ml) was saturated with hydrogen sulfide gas at 0 °C. The mixture was stirred at r.t. overnight. After the evaporated the solvent, the residue was dissolved in anhydrous acetone (5ml) and iodomethane (1ml, 16.6mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the residue was dissolved in anhydrous methanol (5ml) and added a solution of N-methylethylenediamine (0.732ml, 8.3mmol) and acetic acid (1.5ml) in anhydrous methanol (5ml). The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-{4-chloro-2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder. MS found for C<sub>23</sub>H<sub>19</sub>Cl<sub>2</sub>N<sub>5</sub>O<sub>2</sub> M<sup>+</sup>=468 (M+2)<sup>+</sup>=470.

#### Examples 117-141

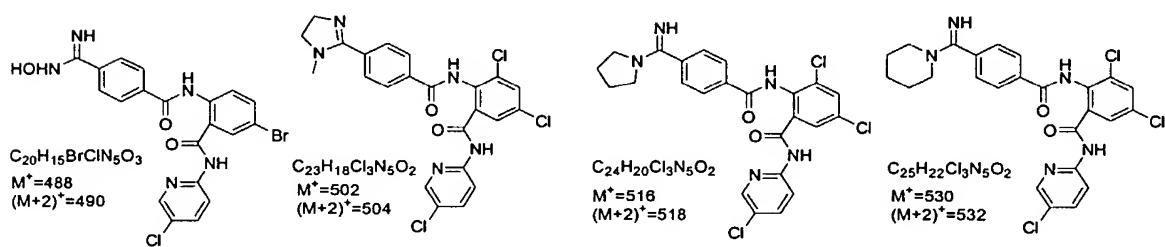
25

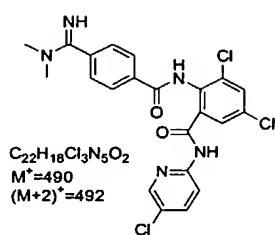
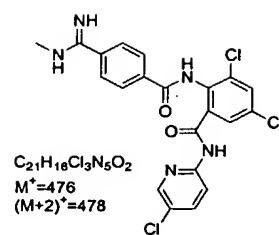
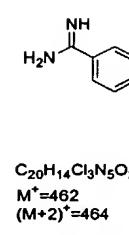
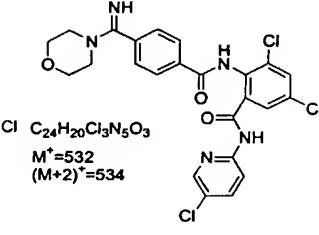
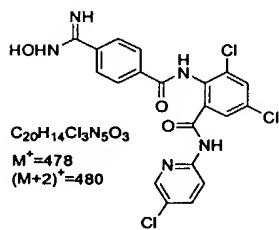
The following compounds were prepared according to the procedure described in example 116.

Example 117Example 118Example 119Example 120

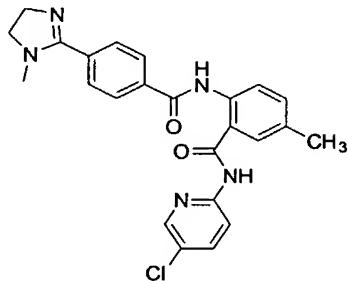
Example 121Example 122Example 123Example 124Example 125Example 126Example 127Example 128Example 129Example 130Example 131Example 132

5

Example 133Example 134Example 135Example 136

Example 137Example 138Example 139Example 140Example 141

5

Example 142

Step 1: To a solution of 5-methyl-2-nitrobenzoic acid (1g, 5.52mmol) in dichloromethane (5ml) was added oxalyl chloride (0.964ml, 11.04mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5ml). 2-amino-5-chloropyridine (852mg, 6.62mmol) and pyridine (1.34ml, 16.56mmol) were

10

added to the solution. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-(5-chloro(2-pyridyl))(5-methyl-2-nitrophenyl)carboxamide as a solid (1.48g, 92%). MS found for  
5 C<sub>13</sub>H<sub>10</sub>ClN<sub>3</sub>O<sub>3</sub> M<sup>+</sup>=291, (M+2)<sup>+</sup>=293.

Step 2: To a solution of the compound of N-(5-chloro(2-pyridyl))(5-methyl-2-nitrophenyl)carboxamide (1.48g, 5.1mmol) in methanol (10ml) was added 5% Pt/C  
10 (1.48g, 0.19mmol). The mixture was applied hydrogen balloon at r.t. for 2 hrs. After the filtration by Celite, the filtrate was concentrated to give (2-aminophenyl)-N-(2-pyridyl)carboxamide, C, chloride, N (1.36g, 100%). MS found for C<sub>13</sub>H<sub>12</sub>ClN<sub>3</sub>O M<sup>+</sup>=262, (M+2)<sup>+</sup>=264.

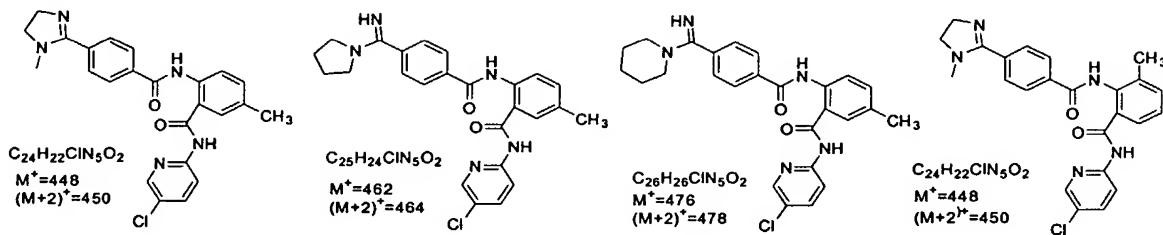
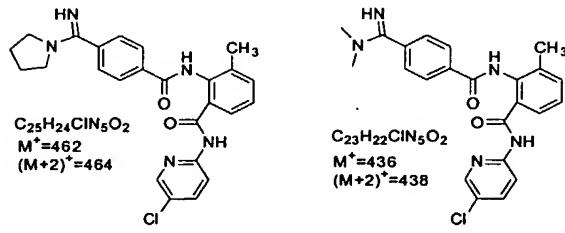
15 Step 3: To a solution of the compound of (2-aminophenyl)-N-(2-pyridyl)carboxamide, C, chloride, N (1.36g, 5.2mmol) in dichloromethane (10ml) was added 3-cyanobenzoyl chloride (860mg, 5.2mmol) and pyridine (1.26ml, 15.6mmol). The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude  
20 residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-[2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl](4-cyanophenyl)carboxamide as a solid (830mg, 41%). MS found for C<sub>21</sub>H<sub>15</sub>ClN<sub>4</sub>O<sub>2</sub> M<sup>+</sup>=390, (M+2)<sup>+</sup>=392.

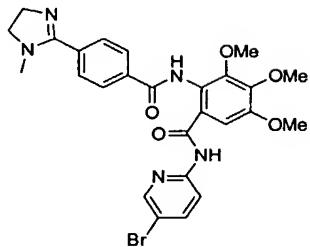
25 Step 4: To a lotion of the compound of N-[2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl](4-cyanophenyl)carboxamide (830mg, 2.1mmol) in anhydrous methanol (5ml) and ethyl acetate (10ml) was saturated with hydrogen chloride gas at 0 °C. The mixture was stirred at r.t. overnight. After the evaporated the solvent, the  
30 residue was dissolved in anhydrous methanol (5ml) and N-methylethylenediamine (0.926ml, 10.5mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-[2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methylphenyl][4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder. MS found for  
35 C<sub>24</sub>H<sub>22</sub>ClN<sub>5</sub>O<sub>2</sub> M<sup>+</sup>=448, (M+2)<sup>+</sup>=450.

Examples 143-148

The following compounds were prepared according to the procedure described in Example 142.

5

Example 143Example 144Example 145Example 146Example 147Example 148

Example 149

Step 1: To a solution of 3,4,5-trimethoxy-2-nitrobenzoic acid (0.5g, 1.95mmol) in dichloromethane (5ml) was added oxalyl chloride (0.34ml, 3.9mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5ml). 2-amino-5-bromopyridine (0.81g, 4.7mmol) and pyridine (0.94ml, 11.7mmol) were added to the solution. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using solvent system 25% ethyl acetate in hexane as eluent to give N-(5-bromo(2-pyridyl))(3,4,5-trimethoxy-2-nitrophenyl)carboxamide as a solid (790mg, 98%). MS found for C<sub>15</sub>H<sub>14</sub>BrN<sub>3</sub>O<sub>6</sub> M<sup>+</sup>=412, (M+2)<sup>+</sup>=414.

15

Step 2: To a solution of the compound of N-(5-bromo(2-pyridyl))(3,4,5-trimethoxy-2-nitrophenyl)carboxamide (790mg, 1.92mmol) in ethyl acetate (5ml) was added tin chloride (II) hydrate (1.73g, 7.67mmol). The mixture was stirred under reflux condition for 2 hrs. After filtered by Celite, the filtrate was added 1N sodium hydroxide solution and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate and concentrated to give (2-amino-3,4,5-trimethoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide (570mg, 77%). MS found for C<sub>15</sub>H<sub>16</sub>BrN<sub>3</sub>O<sub>4</sub> M<sup>+</sup>=382, (M+2)<sup>+</sup>=384.

25

Step 3: To a solution of the compound of (2-amino-3,4,5-trimethoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide (570mg, 1.49mmol) in dichloromethane (5ml) was added 3-cyanobenzoyl chloride (247mg, 1.49mmol) and pyridine (0.362ml, 4.48mmol). The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the crude residue was purified by silica gel column chromatography using

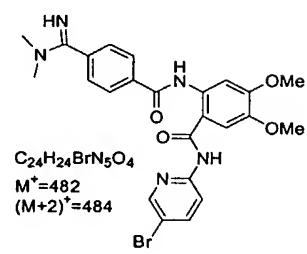
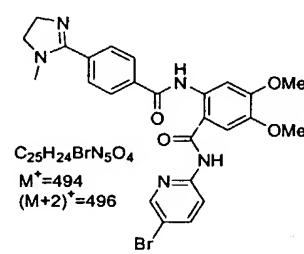
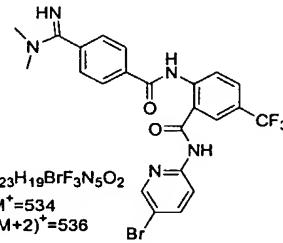
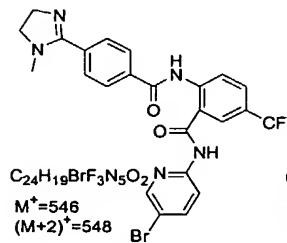
solvent system 25% ethyl acetate in hexane as eluent to give N-[6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl](4-cyanophenyl)carboxamide as a solid (680mg, 69%). MS found for C<sub>23</sub>H<sub>19</sub>BrN<sub>4</sub>O<sub>5</sub> M<sup>+</sup>=511, (M+2)<sup>+</sup>=513.

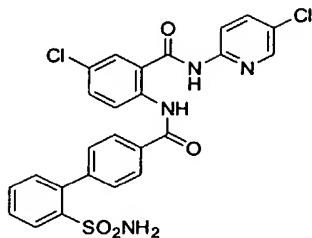
5

Step 4: To a solution of the compound of N-[6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl](4-cyanophenyl)carboxamide (680mg, 1.33mmol) in anhydrous methanol (5ml) and ethyl acetate (10ml) was saturated with hydrogen chloride gas at 0 °C. The mixture was stirred at r.t. overnight. After the evaporation of the solvent, the residue was dissolved in anhydrous methanol (5ml) and N-methylethylenediamine (0.586ml, 6.65mmol) was added. The mixture was stirred under reflux condition for 2 hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-[6-[N-(5-bromo(2-pyridyl))carbamoyl]-2,3,4-trimethoxyphenyl][4-(1-methyl(2-imidazolin-2-yl))phenyl]carboxamide as a white powder (240mg, 32%). MS found for C<sub>26</sub>H<sub>26</sub>BrN<sub>5</sub>O<sub>5</sub> M<sup>+</sup>=568, (M+2)<sup>+</sup>=570.

#### Examples 150-153

The following compounds were prepared according to the procedure described in Example 149.

Example 150Example 151Example 152Example 153

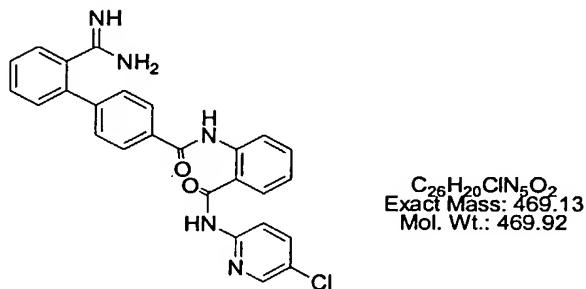
Example 154

Step 1: To a solution of 4-{[(tert-butyl)amino]sulfonyl}phenylbenzoic acid (167mg, 0.5mmol) in dichloromethane (5ml) was added oxalyl chloride (0.09ml, 1mmol) and a few drops of dimethylformamide. The mixture was stirred at r.t. for 2 hrs. After the evaporation of the solvent, the residue was dissolved in dichloromethane (5ml). The compound of (2-amino-5-chlorophenyl)-N-(5-chloro(2-pyridyl))carboxamide (0.17g, 0.6mmol) and pyridine (0.122ml, 1.5mmol) were added to the solution. The mixture was stirred at r.t. overnight. The solvent was evaporated to give (2-{[4-(2-[(tert-butyl)amino]sulfonyl)phenyl]phenyl}-carbonylamino)-5-chlorophenyl-N-(5-chloro(2-pyridyl))carboxamide. MS found for C<sub>29</sub>H<sub>26</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub>S M<sup>+</sup>=597, (M+2)<sup>+</sup>=599.

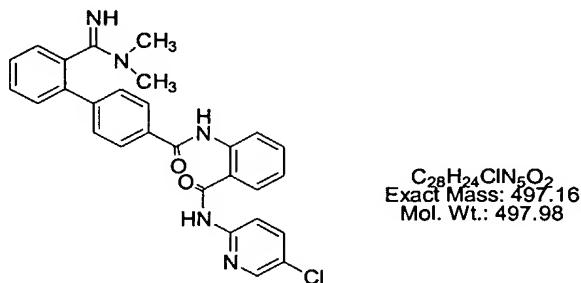
Step 2: The mixture of the compound of (2-{[4-(2-[(tert-butyl)amino]sulfonyl)phenyl]phenyl}-carbonylamino)-5-chlorophenyl-N-(5-chloro(2-pyridyl))carboxamide example 12 (0.5mmol) in trifluoroacetic acid (5ml) was stirred at r.t. for 5hrs. After the evaporation of solvent, the crude residue was purified by RP-HPLC to give N-(5-chloro(2-pyridyl))(5-chloro-2-{[4-(2-sulfamoylphenyl)phenyl]carbonylamino}phenyl)-carboxamide as a white powder (68mg, 25%). MS found for C<sub>25</sub>H<sub>18</sub>Cl<sub>2</sub>N<sub>4</sub>O<sub>4</sub>S M<sup>+</sup>=541, (M+2)<sup>+</sup>=543.

Example 155**2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]-benzenecarboxamidine**

5



A stream of  $H_2S$  (g) was bubbled through a 0 °C solution of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl} [4-(2-cyanophenyl)phenyl]carboxamide (100 mg, 0.22 mmol, 1.0 equiv.) in 9 mL pyridine and 1 mL NEt<sub>3</sub>, until saturation. The mixture was stirred at rt for 1 day and evaporated. The resulting residue was treated with MeI (94 mg, 0.663 mmol, 3.0 equiv.) in 10 mL acetone at reflux temperature for 1 hr and concentrated to dryness. The resulting residue was treated with a mixture of NH<sub>4</sub>OAc (340 mg, 4.42 mmol, 20 equiv.) in 0.5 mL acetic acid and 2 mL methanol at 50 °C for 2 days. The solvent was removed at reduced pressure and the crude benzamidine was purified by HPLC (C18 reversed phase) eluting with 0.1% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN to give 2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]benzenecarboxamidine (15 mg, 15%). MS found for  $C_{26}H_{20}ClN_5O_2$  (M+H)<sup>+</sup>: 470.

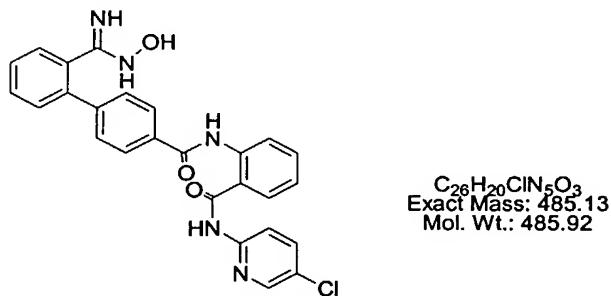
20    Example 156**(4-{2-[(dimethylamino)iminomethyl]phenyl}phenyl)-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide**

This compound was prepared according to the procedure described in Example 155.  
 MS found for  $C_{28}H_{24}ClN_5O_2$  ( $M+H$ )<sup>+</sup>: 498.

5    Example 157

**N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[2-((hydroxyamino)iminomethyl)-phenyl]phenyl}carboxamide**

10

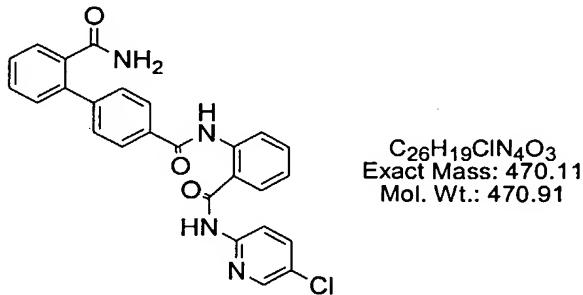


A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}[4-(2-cyanophenyl)phenyl] carboxamide (14 mg, 0.03 mmol, 1.0 equiv.), hydroxyamine hydrochloride (6.25 mg, 0.09 mmol, 3.0 equiv.) and triethyl amine (0.03 mL, 0.3 mmol, 10.0 equiv.) in ethanol (3 mL) was stirred at rt for 6 days, concentrated and 15 HPLC (C18 reversed phase) eluting with 0.1% TFA in  $H_2O/CH_3CN$  to give N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl} {4-[2-((hydroxyamino)iminomethyl) phenyl] phenyl}carboxamide (4 mg, 27.5%).

MS found for  $C_{26}H_{20}ClN_5O_3$  ( $M+H$ )<sup>+</sup>: 486.

20    Example 158

**2-[4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]phenyl}carbamoyl)phenyl]benzamide**

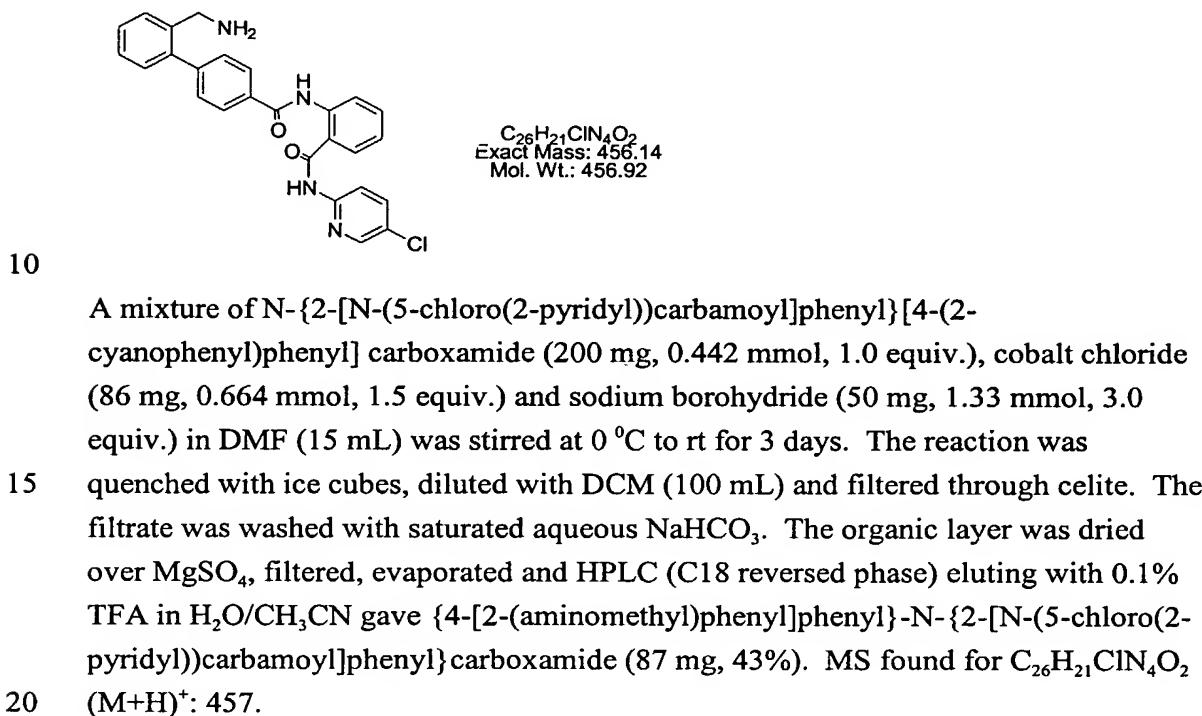


This compound was obtained as one of the side product in Example 157.

MS found for  $C_{26}H_{21}ClN_4O_3$  ( $M+H$ )<sup>+</sup>: 471

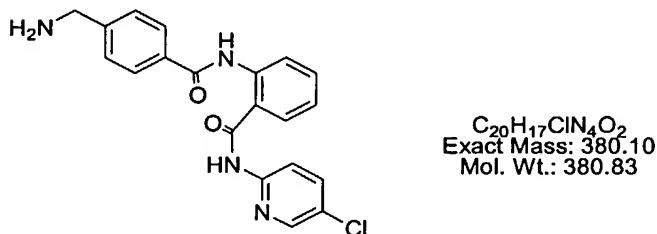
5    Example 159

{4-[2-(aminomethyl)phenyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-phenyl}carboxamide



Example 160**[4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide**

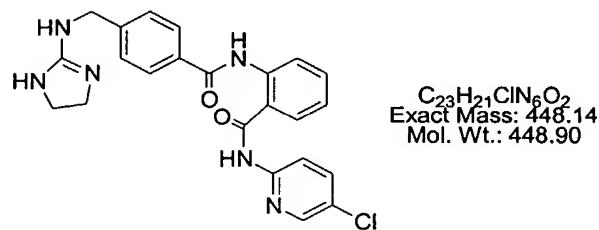
5



A mixture of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-cyanophenyl)carboxamide (1 g, 2.6 mmol, 1.0 equiv.), cobalt chloride (0.5 g, 3.85 mmol, 1.5 equiv.) and sodium borohydride (0.295 g, 7.8 mmol, 3.0 equiv.) in DMF (20 mL) was stirred at 0 °C to rt for 2.5 hr. The reaction was quenched with ice cubes, diluted with ethyl acetate (100 mL) and filtered through celite. The filtrate was washed with saturated aqueous NaHCO<sub>3</sub>. The organic layer was dried over MgSO<sub>4</sub>, filtered, evaporated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN gave [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (320 mg, 30%). MS found for C<sub>20</sub>H<sub>17</sub>ClN<sub>4</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 381.

Example 161

20 **N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[(2-imidazolin-2-ylamino)methyl]-phenyl}carboxamide**



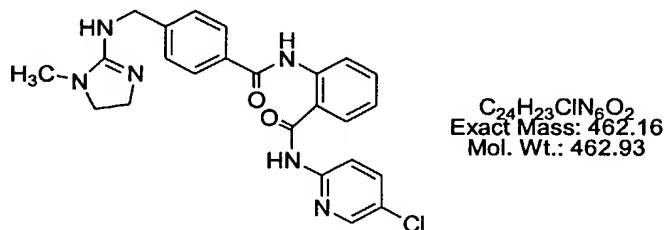
A mixture of [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (80 mg, 0.21 mmol), 2-methylthio-2-imidazoline hydriodide (77 mg, 0.315 mmol, 1.5 equiv.) and triethyl amine (0.5 mL) in 1 mL DMF was stirred at room temperature overnight, concentrated to dryness and 5 HPLC (C18 reversed phase) eluting with 0.1% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN gave N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-[(2-imidazolin-2-ylamino)methyl]phenyl}carboxamide (13.5 mg, 15%). MS found for C<sub>23</sub>H<sub>21</sub>CIN<sub>6</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 449

10

## Example 162

**N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}(4-{{[(1-methyl(2-imidazolin-2-yl)amino)methyl]phenyl}carboxamide}**

15



Step 1: To the boiling solution of 2-methylthio-2-imidazoline hydriodide (1 g, 8.4 mmol) in methanol (10 mL) was added MeI (0.78 mL, 12.6 mmol, 1.5 equiv.) dropwise. The reaction mixture was stirred at reflux temperature for 1 hr, 20 concentrated and crystallized with ether to give 1-methyl-2-methylthio-2-imidazoline (1.1 g, 100%).

MS found for C<sub>5</sub>H<sub>10</sub>N<sub>2</sub>S (M+H)<sup>+</sup>: 131.

Step 2: A mixture of [4-(aminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}carboxamide (74 mg, 0.195 mmol), 1-methyl-2-methylthio-2-imidazoline (25 mg, 0.195 mmol), NEt<sub>3</sub> (2 mL) and pyridine (5 mL) was stirred at 80 °C overnight, concentrated and HPLC (C18 reversed phase) eluting with 0.1% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN gave N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]phenyl}{4-{{[(1-methyl(2-imidazolin-2-

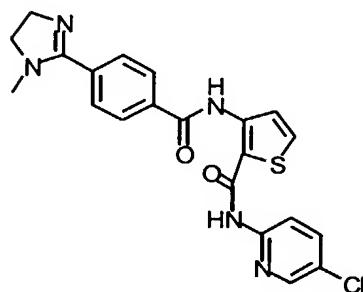
130

yl))amino]methyl}phenyl)carboxamide (52 mg, 65%). MS found for C<sub>24</sub>H<sub>23</sub>CIN<sub>6</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 463.

Example 163

5

**N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(1-methyl(2-imidazolin-2-yl)phenyl]carboxamide**



10

**Preparation of methyl 3-[(4-cyanophenyl)carbonylamino]thiophene-2-carboxylate**

A mixture of 4-cyanobenzoyl chloride (1.0500g, 6.4 mmol), methyl 3-aminothiophenecarboxylate (1.0000g, 6.4 mmol), and triethylamine (1 mL, 7.0 mmol) in dichloromethane was stirred at room temperature for 18 hours. The mixture was poured into a separatory funnel and washed by 1 N HCl. The organic layers were combined, dried over MgSO<sub>4</sub>, concentrated in *vacuo*, and chromatographed through a silica gel column to give the title compound 1.6588 g (91%). ES-MS 287 (M+1).

20

**Preparation of N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}(4-cyanophenyl)carboxamide**

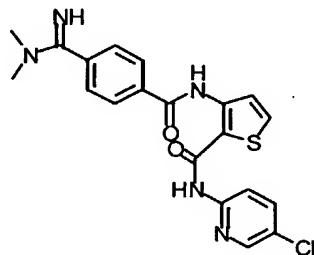
A portion of 2-amino-5-chloropyridine (68.6 mg, 0.5 mmol) was treated with AlMe<sub>3</sub> (0.8 mL, 1.6 mmol), followed by adding the product from step A (160 mg, 0.5 mmol). The mixture was stirred at room temperature for 18 hours. The excess of AlMe<sub>3</sub> was killed by 1N HCl solution. The organic layers were combined, dried over MgSO<sub>4</sub>, concentrated in *vacuo*, and chromatographed through a silica gel column to give the title compound 0.1528 g (80%). ES-MS 383 (M+1).

**Preparation of Example 163.**

A mixture of the product from step B (0.1528 g, 0.4 mmol) and EtOH saturated with  
 5 HCl was stirred at room temperature for 18 hours. The solvent was removed by a rotovap. The crude oil was treated with 2 mL N-methylethylenediamine for 2 hours until the reaction was complete. Prep HPLC was used to purity the final product. It gave 0.1537 g (88%). ES-MS 440(M+1).

10 **Example 164**

**{4-[{(dimethylamino)iminomethyl]phenyl}-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}carboxamide**

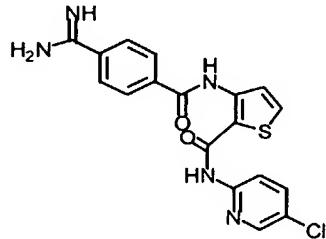


15

Example 164 was made by the procedure of Example 163. ES-MS 428(M+1).

**Example 165**

20 **4-(N-{2-[N-(5-chloro-2-pyridyl)carbamoyl]-3-thienyl}carbamoyl)benzenecarboxamidine**

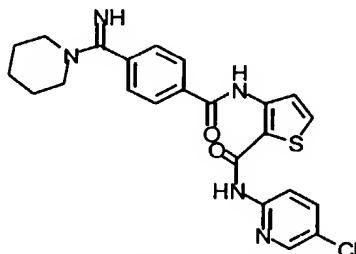


Example 165 was made by the procedure of Example 163. ES-MS 400(M+1).

Example 166

**N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopiperidylmethyl)-phenyl]carboxamide**

5



Example 166 was made by the procedure of Example 163. ES-MS 468(M+1).

Example 167

10    **N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopyrrolidinylmethyl)-phenyl]carboxamide**

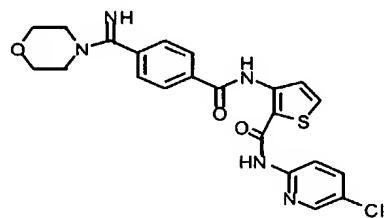


Example 167 was made by the procedure of Example 163. ES-MS 454(M+1).

Example 168

15

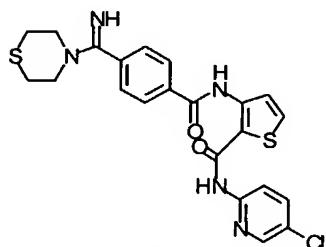
**N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminomorpholin-4-ylmethyl)phenyl]carboxamide**



Example 168 was made by the procedure of Example 163. ES-MS 470(M+1).

Example 169

5    **N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carboxamide**

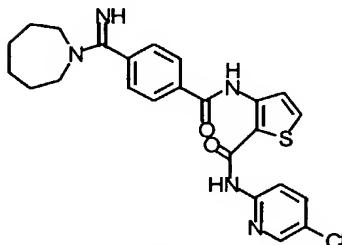


Example 169 was made by the procedure of Example 163. ES-MS 486(M+1).

Example 170

10

**[4-(azaperhydroepinyliminomethyl)phenyl]-N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}carboxamide**

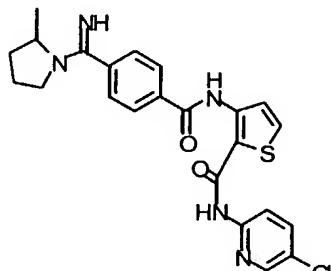


Example 170 was made by the procedure of Example 163. ES-MS 482(M+1).

15

Example 171

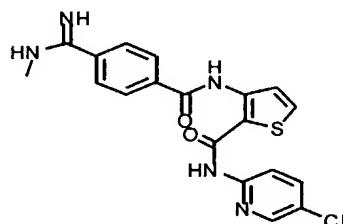
**N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}{4-[imino(2-methylpyrrolidinyl)methyl]phenyl}carboxamide**



5 Example 171 was made by the procedure of Example 163. ES-MS 468(M+1).

Example 172

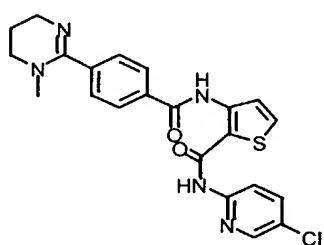
**N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}{4-[imino(methylamino)methyl]phenyl}carboxamide**



Example 172 was made by the procedure of Example 163.

Example 173

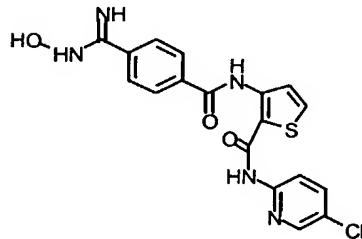
**N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-(3-methyl(3,4,5,6-tetrahydropyrimidin-2-yl))phenyl]carboxamide**



Example 173 was made by the procedure of Example 163. ES-MS 414(M+1).

Example 174

5 N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}[4-((hydroxyamino)iminomethyl)-phenyl]carboxamide



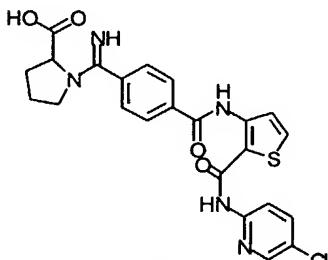
Example 174 was made by the procedure of Example 163. ES-MS 416(M+1).

10

Example 175

15 1-{[4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl](3-thienyl)}carbamoyl)phenyl]-iminomethyl}pyrrolidine-2-carboxylic acid

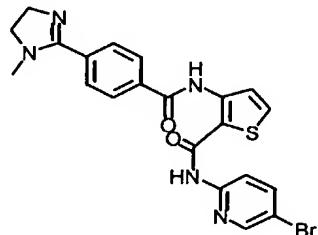
15



Example 175 was made by the procedure of Example 163. ES-MS 498(M+1).

Example 176

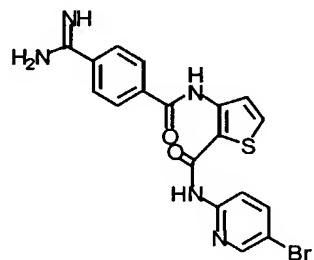
**N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(1-methyl(2-imidazolin-2-yl)phenyl]carboxamide**



5 Example 176 was made by the procedure of Example 163. ES-MS 484(M+1).

Example 177

**4-(N-{2-[N-(5-bromo-2-pyridyl)carbamoyl]-3-thienyl}carbamoyl)benzenecarboxamidine**

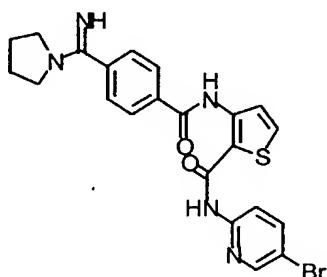


10

Example 177 was made by the procedure of Example 163. ES-MS 444(M+1).

Example 178

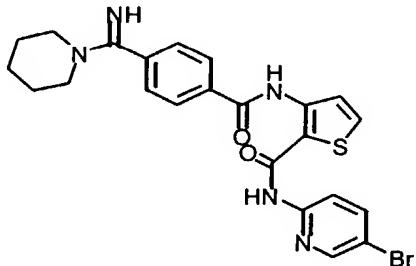
**N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopyrrolidinylmethyl)phenyl]carboxamide**



Example 178 was made by the procedure of Example 163. ES-MS 494(M+1).

Example 179

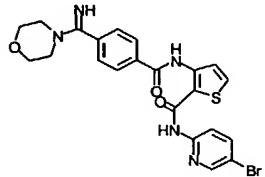
5    **N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminopiperidylmethyl)phenyl]carboxamide**



Example 179 was made by the procedure of Example 163. ES-MS 512(M+1).

Example 180

10    **N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(iminomorpholin-4-ylmethyl)phenyl]carboxamide**

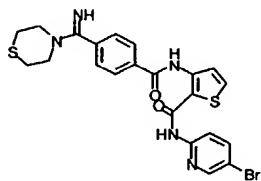


Example 180 was made by the procedure of Example 163. ES-MS 514(M+1).

Example 181

**N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carboxamide**

5

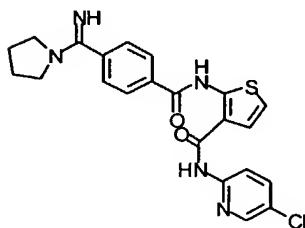


Example 181 was made by the procedure of Example 163. ES-MS 530(M+1).

Example 182

10

**N-{3-[N-(5-chloro(2-pyridyl))carbamoyl](2-thienyl)}[4-(iminopyrrolidinylmethyl)phenyl]carboxamide**



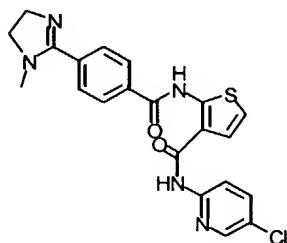
15

Example 182 was made by the procedure of Example 163. ES-MS 454(M+1).

Example 183

20

**N-{3-[N-(5-chloro(2-pyridyl))carbamoyl](2-thienyl)}[4-(1-methyl(2-imidazolin-2-yl)phenyl]carboxamide**

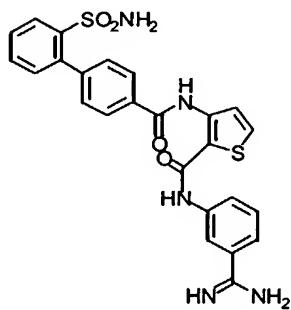


Example 183 was made by the procedure of Example 163. ES-MS 440(M+1).

Example 184

5

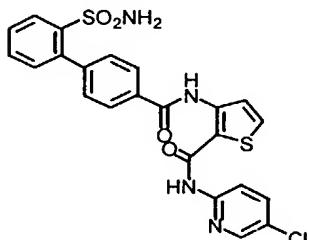
**3-[{3-[(4-(2-sulfamoylphenyl)phenyl]carbonylamino}-2-thienyl]carbonylamino}benzenecarboxamidine**



10 Example 184 was made by the procedure of Example 163 (step A, B, C) followed by a final step of trifluoroacetic acid removal of the *t*-butyl group. 4-(2-{{[(tert-butyl)amino]sulfonyl}phenyl}benzoyl chloride was used to replace 4-cyanobenzoyl chloride in Example 1. ES-MS 520(M+1).

15 Example 185

**N-{2-[N-(5-chloro(2-pyridyl)carbamoyl](3-thienyl)}[4-(2-sulfamoylphenyl)phenyl]carboxamide**



20

Example 185 was made by the procedure of Example 163 except using 4-(2-{{(tert-butyl)amino}sulfonyl}phenyl)benzoyl chloride instead of 4-cyanobenzoyl chloride. ES-MS 513(M+1).

5    Example 186

N-{2-[N-(5-bromo(2-pyridyl))carbamoyl](3-thienyl)}[4-(2-sulfamoylphenyl)phenyl]carboxamide



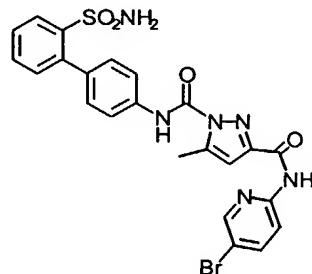
10

Example 186 was made by the procedure of Example 185. ES-MS 556(M+1).

Example 187

15

N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylaminocarbonyl)5-methyl-pyrazolcarboxamide.



20

Step 1: A solution of 2-amino-5-bromopyridine (0.200 g, 1.16 mmol 1.0 equiv), in 5 mls of methylene chloride, under argon, was treated with trimethylaluminum (0.312 mL, 2.0N in hexanes, 4.0 equiv) at room temperature for 30 min. To the solution was added ethyl-3-methylpyrazole-5-carboxylate (0.356 g, 2.0 equiv). After 4hrs, the volatile was evaporated, and the residue was redissolved into EtOAc, washed with

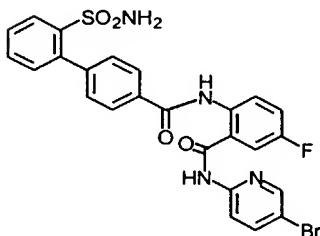
0.5N HCl, 0.2 N K<sub>2</sub>CO<sub>3</sub>, and saturated aqueous NaCl. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, evaporated and purified via flash chromatography on silica gel to give N-(5-bromo-2-pyridinyl)-(3-methyl)5-pyrazolecarboxamide (0.160 g, 49%). MS found for C<sub>10</sub>H<sub>9</sub>BrN<sub>4</sub>O (M+H)<sup>+</sup>: 281, 283.

5

Step 2: A solution of N-(5-bromo-2-pyridinyl)-(3-methyl)5-pyrazolecarboxamide (0.060 g, 0.213 mmol, 1.0 equiv) in 2 mL of acetonitrile was treated with triphosgene (0.063 g, 1.0 equiv) at room temperature for 5min under argon. To the solution was added 4-[(2-t-butylaminosulfonyl)phenyl]phenylamine (0.071 g, 1.1 equiv) After 1 hr, the volatile was evaporated and the residue was redissolved into EtOAc, washed with 0.5N HCl, 0.2 N K<sub>2</sub>CO<sub>3</sub>, and saturated aqueous NaCl. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, evaporated, purified via flash chromatography on silica gel and then reacted in 2 mL of trifluoroacetic acid for 16 hrs at room temperature. TFA was then evaporated and the residue was redissolved into EtOAc, washed with 0.5N HCl, 0.2 N K<sub>2</sub>CO<sub>3</sub>, and saturated aqueous NaCl. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, evaporated, and triturated with diethyl ether to give N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl] phenylaminocarbonyl)5-methyl-pyrazolcarboxamide (0.0024 g, 2%). MS found for C<sub>23</sub>H<sub>19</sub>BrN<sub>6</sub>O<sub>4</sub>S (M+H)<sup>+</sup>: 555, 557.

10      20      Example 188

**N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylcarbonylamino)-5-fluorophenylcarboxamide.**



25

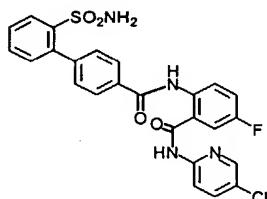
Step 1: A solution of 5-fluoro-2-nitrobenzoic acid (10.0 g, 54 mmol, 1.0 equiv), 2-amino-5-bromopyridine (12.2 g, 1.3 equiv), in 80 mL of pyridine was treated with phosphorous oxychloride (25.3 g, 3.0 equiv) for 30 min. The volatile was evaporated

and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated. The volatile was evaporated, and the product was triturated with diethyl ether to give N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (12.5 g, 68%). MS found for C<sub>12</sub>H<sub>7</sub>BrFN<sub>3</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 340, 342.

Step 2: A solution of N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (2.0 g, 5.88 mmol, 1.0 equiv) in 30 mL of EtOAc was treated with SnCl<sub>2</sub>·2H<sub>2</sub>O (5.90 g, 4 equiv) at reflux for 4 h. The volatile was evaporated and the residue was redissolved in EtOAc, washed with saturated aqueous NaHCO<sub>3</sub>, and 1N NaOH. The organic layer was dried over MgSO<sub>4</sub>, filtered and evaporated to N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (1.79 g, 98%). MS found for C<sub>12</sub>H<sub>9</sub>BrFN<sub>3</sub>O (M+H)<sup>+</sup>: 310, 312.

Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (0.310 g, 1 mmol, 1.0 equiv), 4-[(2-t-butylaminosulfonyl)phenyl]benzoyl chloride (0.430 g, 1.3 equiv), pyridine (2 mL) in 10 mL of dichloromethane was stirred at rt overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated. The intermediate was reacted into 5 mL of trifluoroacetic acid at rt overnight. TFA was then evaporated and the product was triturated with diethyl ether, and then with chloroform to give N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl] phenylcarbonylamino)-5-fluorophenylcarboxamide (120 mg, 21%). MS found for C<sub>25</sub>H<sub>18</sub>BrFN<sub>4</sub>O<sub>4</sub>S (M+H)<sup>+</sup>: 569, 571.

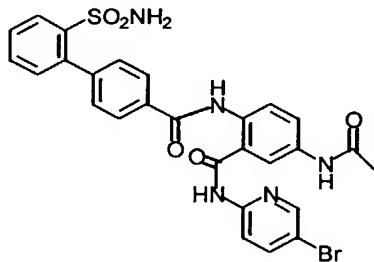
#### Example 189



This compound is prepared according to the procedure described in example 2 with the exception of using zinc in acetic acid to reduce nitro-intermediate in step 2. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN. MS found for C<sub>25</sub>H<sub>18</sub>ClFN<sub>4</sub>O<sub>4</sub>S (M+H)<sup>+</sup>: 525, 527.

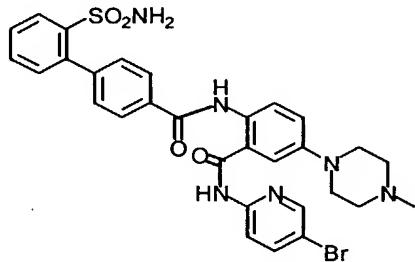
5

Example 190



This compound is prepared according to the procedure described in example 2 with  
10 the exception of using 5-acetamido-2-nitrobenzoic acid as the starting material in step  
1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5%  
TFA in H<sub>2</sub>O/CH<sub>3</sub>CN. MS found for C<sub>27</sub>H<sub>22</sub>BrN<sub>5</sub>O<sub>5</sub>S (M+H)<sup>+</sup>: 608, 610.

Example 191



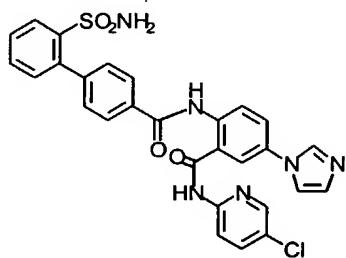
15

This compound is prepared according to the procedure described in example 2 with  
the exception of the following step 1b performed on the nitro-intermediate from step  
1. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5%  
20 TFA in H<sub>2</sub>O/CH<sub>3</sub>CN. MS found for C<sub>30</sub>H<sub>29</sub>BrN<sub>6</sub>O<sub>4</sub>S (M+H)<sup>+</sup>: 649, 651.

Step 1b: A mixture of N-(5-bromo-2-pyridinyl)-(2-nitro)-5-fluorophenylcarboxamide (0.68 g, 2 mmol, 1.0 equiv), N-methylpiperazine (0.60 g, 3 equiv), and Cs<sub>2</sub>CO<sub>3</sub> (1.30 g, 2 equiv) in 5 mL of dimethylformamide was stirred at 90°C overnight. Ethyl acetate was added and washed with H<sub>2</sub>O. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, 5 evaporated, purified via flash chromatography on silica gel to give N-(5-bromo-2-pyridinyl)-(2-nitro)-5-(4-N-methylpiperazine)phenylcarboxamide (0.54g, 65%). MS found for C<sub>17</sub>H<sub>18</sub>BrN<sub>5</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 419, 421.

Example 192

10



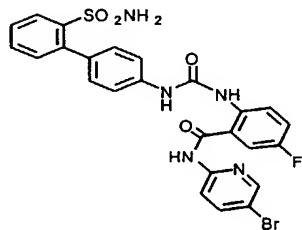
This compound is prepared according to the procedure described in example 5. The final product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN MS found for C<sub>28</sub>H<sub>21</sub>ClN<sub>6</sub>O<sub>4</sub>S (M+H)<sup>+</sup>: 573, 575.

15

Example 193

**N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl]phenylaminocarbonylamino)-5-fluorophenylcarboxamide.**

20

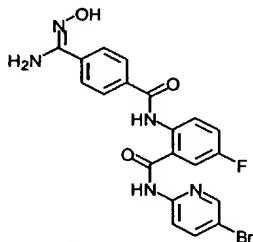


Step 3: A mixture of 4-[(2-t-butylaminosulfonyl)phenyl]phenylamine (0.180 g, 1.2 equiv), N,N'-disuccinimidyl carbonate (0.154 g, 1.2 equiv), 4-methylmorpholine (0.5

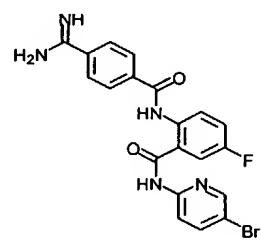
mL) in 10 mL of acetonitrile was stirred at rt for 30 min. N-(5-bromo-2-pyridinyl)-(2-amino)-5-fluorophenylcarboxamide (0.155 g, 0.5 mmol, 1.0 equiv) was added and the solution was stirred at rt for 3 hrs. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO<sub>3</sub> and 5 saturated aqueous NaCl. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated. The intermediate was reacted into 5 mL of trifluoroacetic acid at rt overnight. TFA was then evaporated and the product was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN to give N-(5-bromo-2-pyridinyl)-(2-4-[(2-aminosulfonyl)phenyl] phenylaminocarbonylamino)-5-fluorophenylcarboxamide (0.053 g, 18%). MS found for C<sub>25</sub>H<sub>19</sub>BrFN<sub>5</sub>O<sub>4</sub>S (M+H)<sup>+</sup>: 584, 586.

#### Examples 194-195

15 **N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)5-fluorophenylcarboxamide.**



Example 194



Example 195

Step 1: A mixture of N-(5-bromo-2-pyridinyl)-(2-amino)5-fluorophenylcarboxamide (1.24 g, 4 mmol, 1.0 equiv), 4-cyano benzoyl chloride (0.792 g, equiv), and pyridine 20 (3 mL) in 15 mL of dichloromethane was stirred at rt overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO<sub>3</sub> and saturated aqueous NaCl. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.14 g, 65%). MS found for 25 C<sub>20</sub>H<sub>12</sub>BrFN<sub>4</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 439, 441.

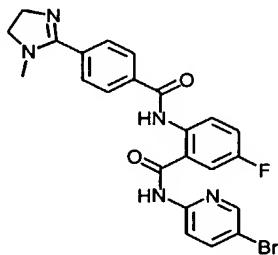
Step 2: A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.12 g, 2.56 mmol, 1.0 equiv), hydroxylamine-HCl (0.213 g, 1.2 equiv), and triethylamine (1 mL) in 15 mL of ethyl alcohol was stirred at 50°C

overnight. The volatile was evaporated and the residue was redissolved into EtOAc, washed with 1N HCl, saturated aqueous NaHCO<sub>3</sub>, and saturated aqueous NaCl. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and evaporated to give N-(5-bromo-2-pyridinyl)-(2-(4-hydroxyamidinophenylcarbonyl)amino)5-fluorophenylcarboxamide (compound Example 194) (0.84 g, 70%). One third of this material was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN to yield 0.20 grams (71%). MS found for C<sub>20</sub>H<sub>15</sub>BrFN<sub>5</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 472, 474.

Step 3: A mixture of N-(5-bromo-2-pyridinyl)-(2-(4-hydroxyamidinophenylcarbonyl)amino)5-fluorophenylcarboxamide (0.56 g, 1.19 mmol, 1.0 equiv) and zinc dust (0.39 g, 5.0 equiv), in 10 mL of acetic acid was stirred at rt for 45 min. The volatile was filtered and evaporated. The residue was purified by HPLC (C18 reversed phase) eluting with 0.5% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN give N-(5-bromo-2-pyridinyl)-(2-(4-amidinophenylcarbonyl)amino)5-fluorophenyl-carboxamide (compound Example 195) (0.24 g, 44%).  
MS found for C<sub>20</sub>H<sub>15</sub>BrFN<sub>5</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 456, 458.

#### Example 196

N-(5-bromo-2-pyridinyl)-(2-(4-(1-methyl-2-imadazolin-2-yl)phenylcarbonyl)amino)5-fluorophenylcarboxamide.



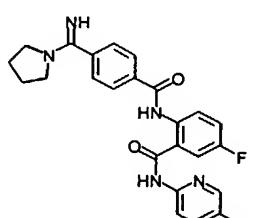
Step 1: A stream of HCl(g) was bubbled through a 0°C solution of N-(5-bromo-2-pyridinyl)-(2-(4-cyanophenylcarbonyl)amino)5-fluorophenylcarboxamide (1.0 g, 2.3 mmol) in 30 mL of methanol until saturation. The mixture was stirred at rt overnight and evaporated. One-fifth of the resulting residue was treated with (2-aminoethyl)methylamine (0.10 g) in 10 ml methanol at rt overnight. The solvent was removed at reduced pressure and the crude product was purified by HPLC (C18

reversed phase) eluting with 0.5% TFA in H<sub>2</sub>O/CH<sub>3</sub>CN to give N-(5-bromo-2-pyridinyl)-(2-(4-(1-methyl-2-imadazolin-2-yl)phenylcarbonyl)amino)5-fluorophenylcarboxamide (0.082 g, 37%). MS found for C<sub>23</sub>H<sub>19</sub>BrFN<sub>5</sub>O<sub>2</sub> (M+H)<sup>+</sup>: 496, 498.

5

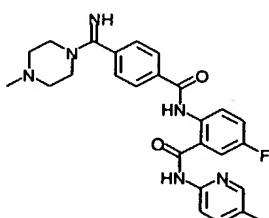
Examples 197-267

The following compounds were prepared generally according to the procedure described in Example 196.



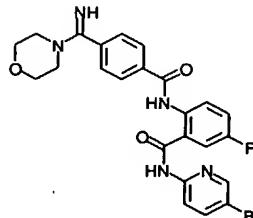
MS (M+H):  
510, 512

Example 197



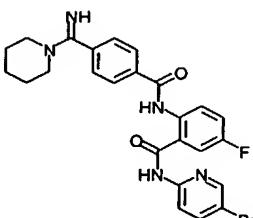
MS (M+H):  
539, 541

Example 198



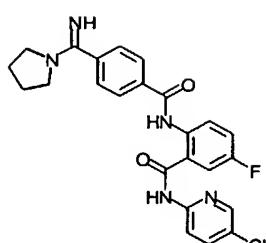
MS (M+H):  
526, 528

Example 199

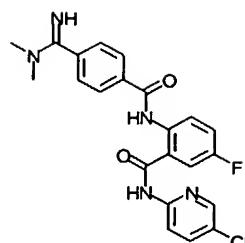


MS (M+H):  
524, 526

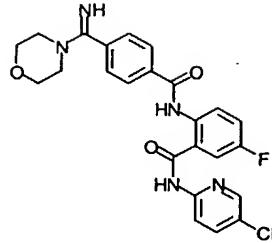
Example 200



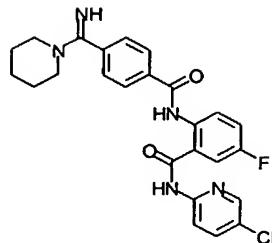
**MS (M+H):**  
466, 468



**MS (M+H):**  
440, 442



**MS (M+H):**  
482, 484



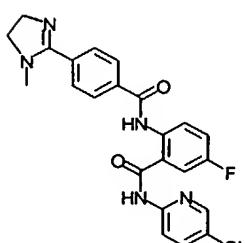
**MS (M+H):**  
480, 482

Example 201

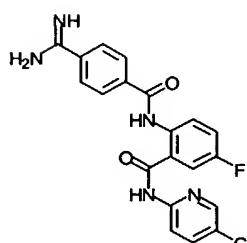
Example 202

Example 203

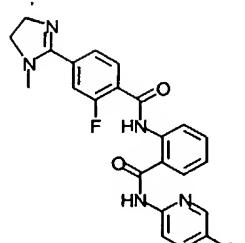
Example 204



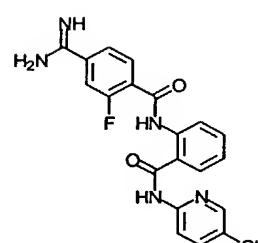
**MS (M+H):**  
452, 454



**MS (M+H):**  
412, 414



**MS (M+H):**  
452, 454



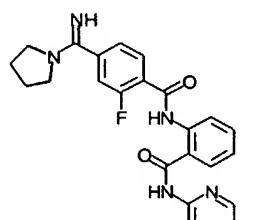
**MS (M+H):**  
412, 414

Example 205

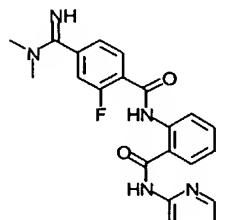
Example 206

Example 207

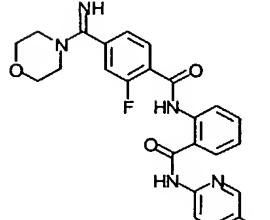
Example 208



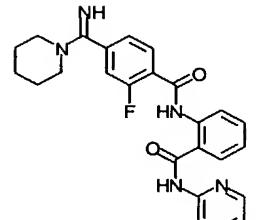
**MS (M+H):**  
466, 468



**MS (M+H):**  
440, 442



**MS (M+H):**  
482, 484



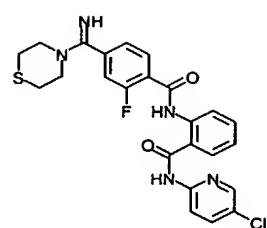
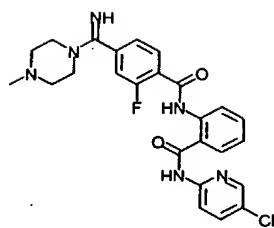
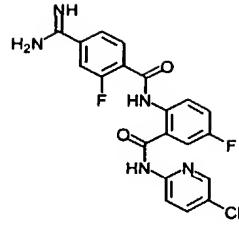
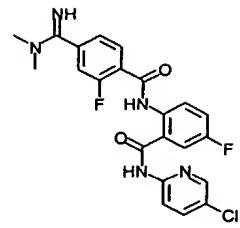
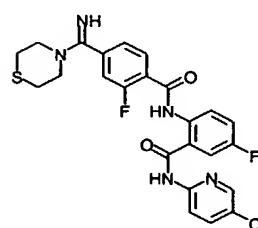
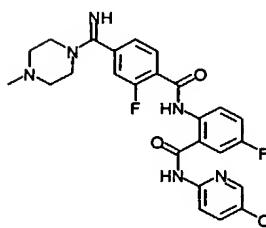
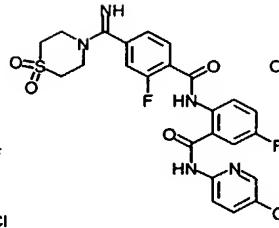
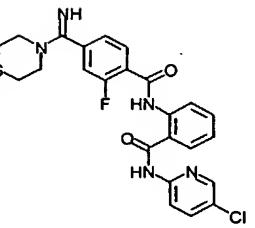
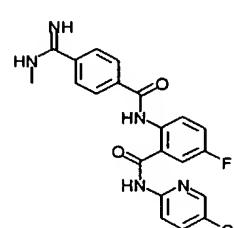
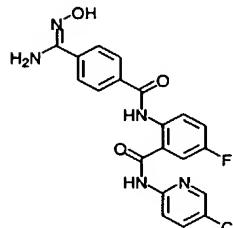
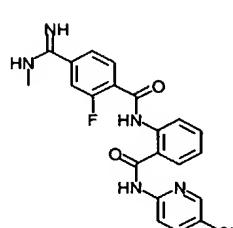
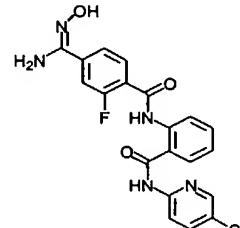
**MS (M+H):**  
480, 482

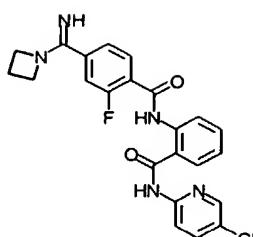
Example 209

Example 210

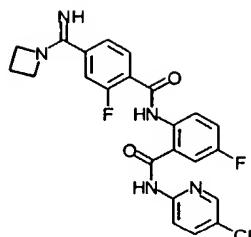
Example 211

Example 212

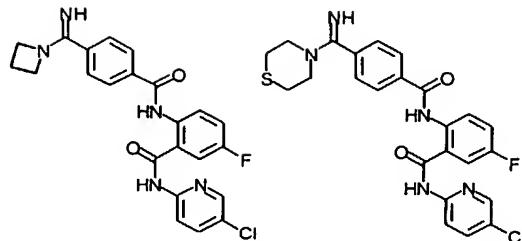
MS (M+H):  
498, 500MS (M+H):  
495, 497MS (M+H):  
430, 432MS (M+H):  
458, 460Example 213Example 214Example 215Example 216MS (M+H):  
516, 518MS (M+H):  
513, 515MS (M+H):  
548, 550MS (M+H):  
530, 532Example 217Example 218Example 219Example 220MS (M+H):  
426, 428MS (M+H):  
428, 430MS (M+H):  
426, 428MS (M+H):  
428, 430Example 221Example 222Example 223Example 224



MS (M+H):  
452, 454



MS (M+H):  
470, 472



MS (M+H):  
452, 454

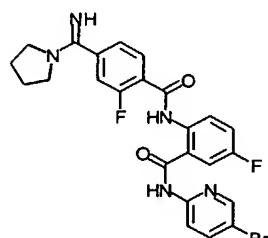
MS (M+H):  
498, 500

Example 225

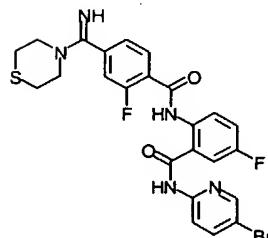
Example 226

Example 227

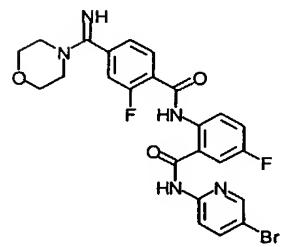
Example 228



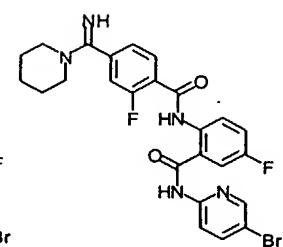
MS (M+H):  
528, 530



MS (M+H):  
560, 562



MS (M+H):  
544, 546



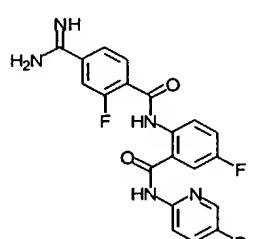
MS (M+H):  
542, 544

Example 229

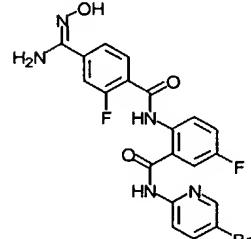
Example 230

Example 231

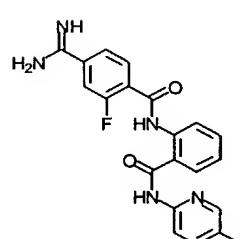
Example 232



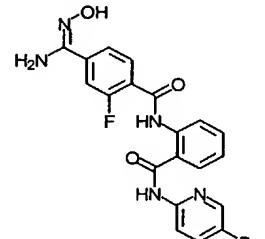
MS (M+H):  
474, 476



MS (M+H):  
490, 492



MS (M+H):  
456, 458



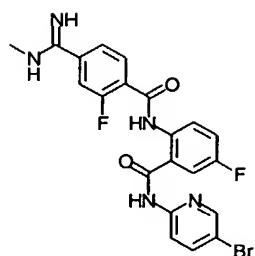
MS (M+H):  
472, 474

Example 233

Example 234

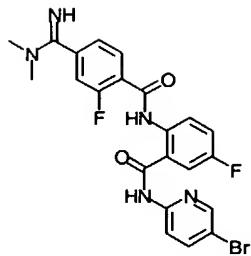
Example 235

Example 236



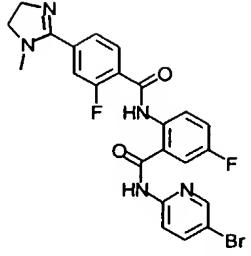
MS (M+H):  
488, 490

Example 237



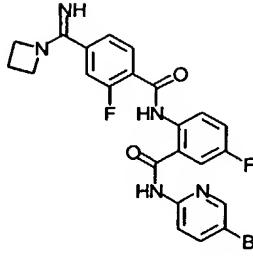
MS (M+H):  
502, 504

Example 238



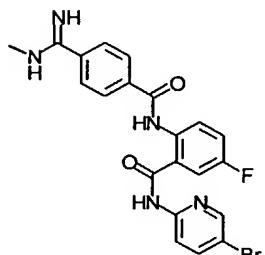
MS (M+H):  
514, 516

Example 239



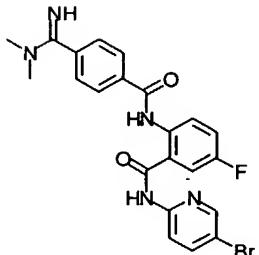
MS (M+H):  
514, 516

Example 240



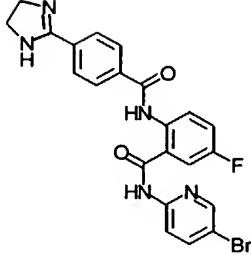
MS (M+H):  
470, 472

Example 241



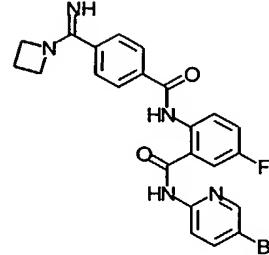
MS (M+H):  
484, 486

Example 242



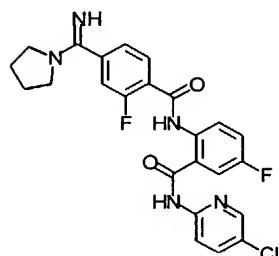
MS (M+H):  
482, 484

Example 243



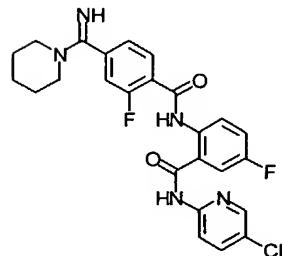
MS (M+H):  
496, 498

Example 244



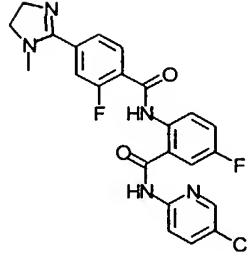
MS (M+H):  
484, 486

Example 245



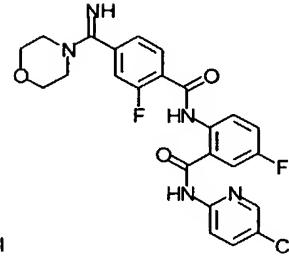
MS (M+H):  
498, 500

Example 246



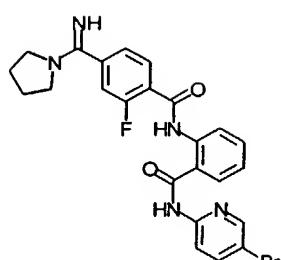
MS (M+H):  
470, 472

Example 247

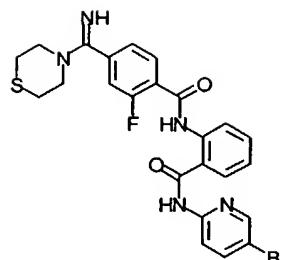


MS (M+H):  
500, 502

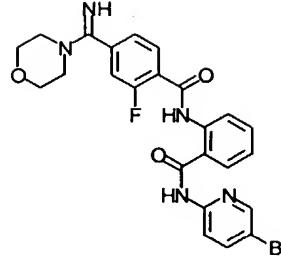
Example 248



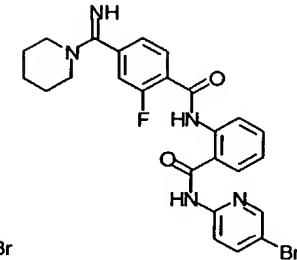
**MS (M+H):**  
510, 512



**MS (M+H):**  
542, 544



**MS (M+H):**  
526, 528



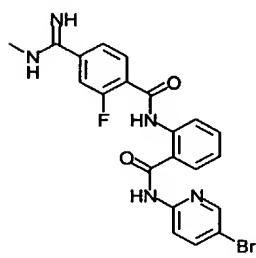
**MS (M+H):**  
524, 526

Example 249

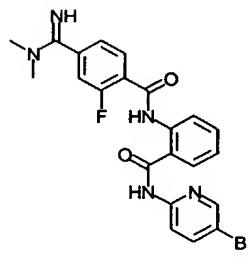
Example 250

Example 251

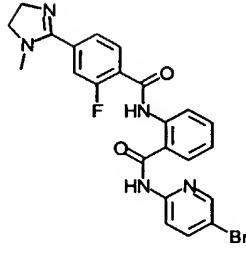
Example 252



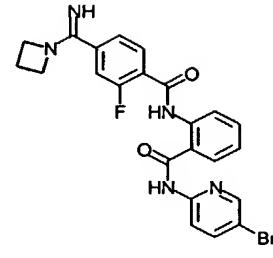
**MS (M+H):**  
470, 472



**MS (M+H):**  
484, 486



**MS (M+H):**  
496, 498



**MS (M+H):**  
496, 498

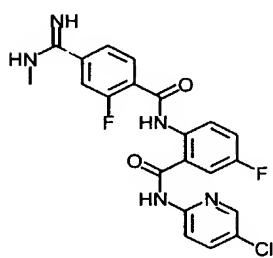
Example 253

Example 254

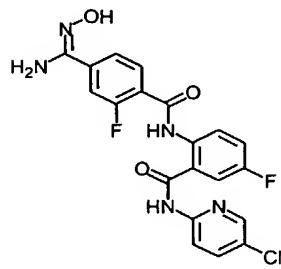
Example 255

Example 256

5



**MS (M+H):**  
444, 446



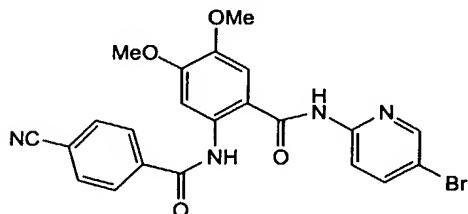
**MS (M+H):**  
446, 448

Example 257

Example 258

Example 259**N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4,5-dimethoxyphenyl}(4-cyanophenyl)carboxamide**

5



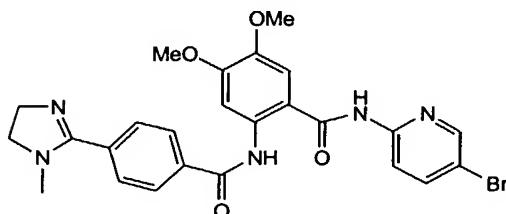
To a solution of 4,5-dimethoxy-2-nitrobenzoic acid (2.2gm, 10mmol) and 2-amino-5-bromopyridine (2.4gm, 14mmol) in anhydrous pyridine (50mL) at 0°C was added  $\text{POCl}_3$  (1.9mL, 20mmol). After stirring at room temperature for 30min, the reaction 10 was complete. The mixture was concentrated and diluted with EtOAc (200mL). The organic solution was washed with brine, dried and evaporated to give intermediate compound 1 (3.0gm, 80%). MS found for  $\text{C}_{14}\text{H}_{12}\text{BrN}_3\text{O}_5$  ( $\text{M}+\text{H}$ ) $^+$ : 382.00, 383.95.

15 A mixture of intermediate compound 1 (320mg, 0.83mmol) and  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  (900mg, 4.0mmol) in EtOAc (10mL) was refluxed for 1 hour. Reduction completed. The solid was filtered through a celite bed. The filtrate was diluted with EtOAc (50mL), and the red solution was washed with 1N aq. NaOH solution (x3) and brine, dried and evaporated to give intermediate compound 2 (230mg, 78%). MS found for  $\text{C}_{14}\text{H}_{14}\text{BrN}_3\text{O}_3$  ( $\text{M}+\text{H}$ ) $^+$ : 352.00, 354.05.

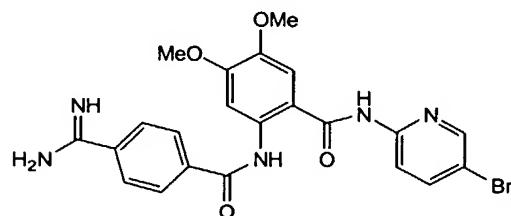
20 To a solution of intermediate compound 2 (200mg, 0.57mmol) in a mixture of pyridine (3mL) and DCM (10mL) was added 4-cyanobenzoyl chloride (140mg, 0.85mmol). Precipitate formed immediately and the reaction was complete. The solid was collected by filtration and washed with DCM. After drying in vacco, the titled 25 compound was obtained as a yellow solid in 70% yield (190mg). MS found for  $\text{C}_{22}\text{H}_{17}\text{BrN}_4\text{O}_4$  ( $\text{M}+\text{H}$ ) $^+$ : 481.00, 483.00.

Example 260**(4,5-dimethoxy-2-{[4-(1-methyl(2-imidazolin-2-yl)phenyl]carbonylamino}phenyl)-N-(5-bromo(2-pyridyl))carboxamide**

5



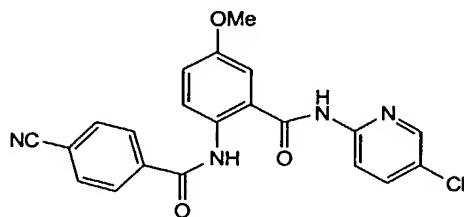
To a solution of compound obtained in Example 259 (100mg, 0.20mmol) in 10% Et<sub>3</sub>N/pyridine (10mL) at 0°C was bubbled dry H<sub>2</sub>S gas to saturation. The mixture was stirred at ambient temperatures overnight, and the conversion was complete. The solvent was removed to dryness, and the residue was suspended in anhydrous acetone (10mL), followed by addition of MeI (1mL). The reaction mixture was refluxed for 1 hour. The solvent was removed by rotary evaporation. To the residue was added anhydrous MeOH (10mL) and N-methylethylenediamine (1mL). The resulting mixture was refluxed for 1 hour, concentrated and subjected to RP-HPLC purification to give the title compound. MS found for C<sub>25</sub>H<sub>24</sub>BrN<sub>5</sub>O<sub>4</sub> (M+H)<sup>+</sup>: 538.1, 540.1.

Example 261**4-(N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4,5-dimethoxyphenyl}carbamoyl)-benzenecarboxamidine**

The title compound was obtained from the Example 259 compound according to the procedure described in Example 2. MS found for C<sub>22</sub>H<sub>20</sub>BrN<sub>5</sub>O<sub>4</sub> (M+H)<sup>+</sup>: 498.1, 500.0.

Example 262

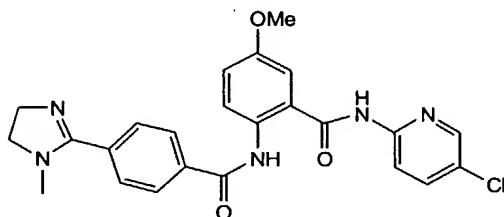
5      **N-(5-chloro(2-pyridyl)){2-[{(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}-carboxamide**



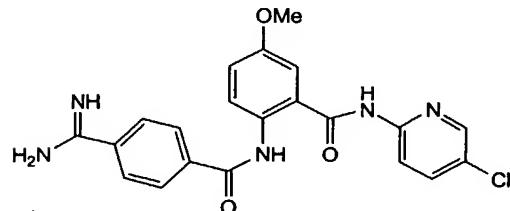
This compound was obtained from 5-methoxy-2-nitrobenzoic acid and 2-amino-5-chloro-pyridine according to the procedure described in Example 259. MS found for  
10 C<sub>21</sub>H<sub>15</sub>ClN<sub>4</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 407.0.

Example 263

15      **N-(5-chloro(2-pyridyl))(5-methoxy-2-{[4-(1-methyl(2-imidazolin-2-yl))phenyl}-carbonylamino}phenyl)carboxamide**



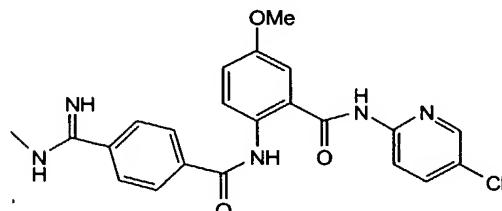
To the suspension of the compound Example 262 (100mg) in a mixture of anhydrous MeOH (5mL) and EtOAc (5mL) at 0°C was bubbled anhydrous HCl gas to saturation.  
20      The mixture was stirred at ambient temperatures overnight. The conversion completed. The solvent was evaporated to dryness. The residue was dissolved in anhydrous MeOH (10mL), followed by addition of N-methylethylenediamine (1mL). The resulting mixture was refluxed for 1 hour, concentrated and subjected to RP-HPLC purification to give the title compound 263. MS found for C<sub>24</sub>H<sub>22</sub>ClN<sub>5</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 464.

Example 264**4-(N-{2-[N-(5-chloro(2-pyridyl))carbamoyl]-4-methoxyphenyl}carbamoyl)benzene-carboxamidine**

The title compound was obtained from the Example 262 compound by procedures according to Example 262. MS found for  $C_{21}H_{18}ClN_5O_3$  ( $M+H$ )<sup>+</sup>: 424.

Example 265

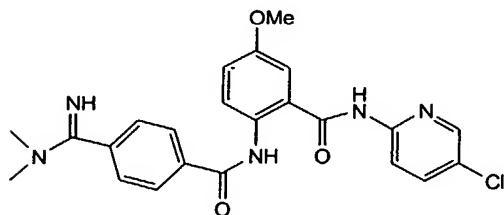
10

**N-(5-chloro(2-pyridyl))[2-(4-[imino(methylamino)methyl]phenyl)carbonylamino]-5-methoxyphenyl]carboxamide**

The title compound was obtained from N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide and methylamine according to the procedure described in Example 262. MS found for  $C_{22}H_{20}ClN_5O_3$  ( $M+H$ )<sup>+</sup>: 438.

Example 266

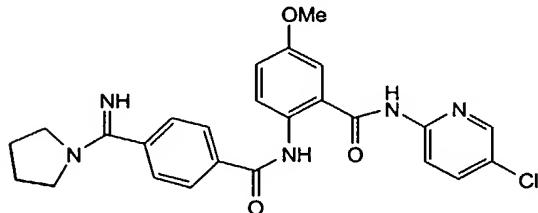
5 [2-((4-[(dimethylamino)iminomethyl]phenyl)carbonylamino)-5-methoxyphenyl]-  
N-(5-chloro(2-pyridyl))carboxamide



The title compound was obtained from N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide and dimethylamine  
10 according to the procedure described in example 263. MS found for C<sub>23</sub>H<sub>22</sub>ClN<sub>5</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 452.

Example 267

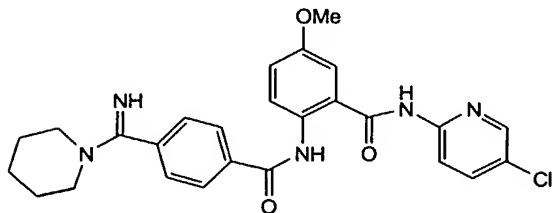
15 N-(5-chloro(2-pyridyl))(2-{{[4-(iminopyrrolidinylmethyl)phenyl]carbonylamino}-  
5-methoxyphenyl)carboxamide



The title compound was obtained from N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide and pyrrolidine  
20 according to the procedure described in Example 263. MS found for C<sub>25</sub>H<sub>24</sub>ClN<sub>5</sub>O<sub>3</sub> (M+H)<sup>+</sup>: 478.

Example 268

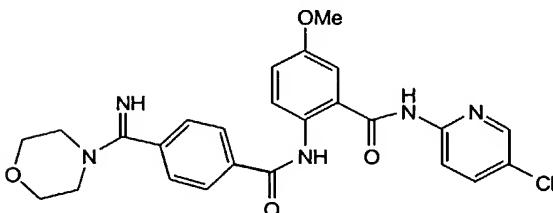
5      **N-(5-chloro(2-pyridyl))(2-{{[4-(iminopiperidylmethyl)phenyl]carbonylamino}-5-methoxyphenyl}carboxamide**



The title compound was obtained from N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide and piperidine  
10 according to the procedure described in Example 263. MS found for  $C_{26}H_{26}ClN_5O_3$  ( $M+H$ )<sup>+</sup>: 492.

Example 269

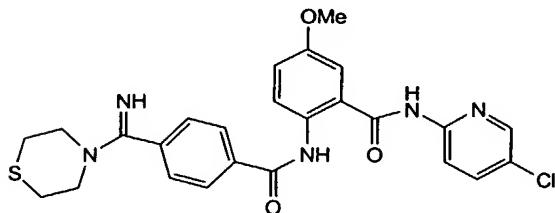
15      **N-(5-chloro(2-pyridyl))(2-{{[4-(iminomorpholin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl}carboxamide**



The title compound was obtained from N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide and morpholine  
20 according to the procedure described in Example 263. MS found for  $C_{25}H_{24}ClN_5O_4$  ( $M+H$ )<sup>+</sup>: 494.1.

Example 270

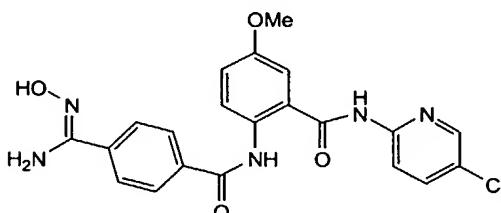
5      **N-(5-chloro(2-pyridyl))(2-{{[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl}carboxamide**



The title compound was obtained from N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide and thiomorpholine  
10 according to the procedure described in Example 263. MS found for  $C_{25}H_{24}ClN_5O_3S$  ( $M+H$ ) $^+$ : 510.

Example 271

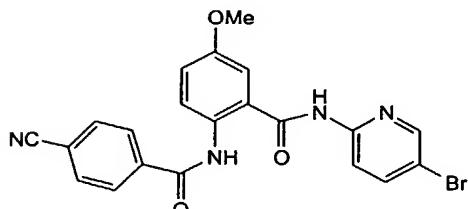
15      **(2-{{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-5-methoxyphenyl)-N-(5-chloro(2-pyridyl))carboxamide**



To a suspension of compound N-(5-chloro(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide (150mg) in EtOH  
20 (10mL) was added hydroxyamine hydrochloride (80mg) and Et<sub>3</sub>N (200μL). The mixture was stirred at 60°C overnight and the reaction was complete. The solvent was evaporated and the crude material was purified by RP-HPLC to give the title compound. MS found for  $C_{21}H_{18}ClN_5O_4$  ( $M+H$ ) $^+$ : 440.1.

Example 272

5   **N-(5-bromo(2-pyridyl)){2-[(4-cyanophenyl)carbonylamino]-5-methoxyphenyl}carboxamide**

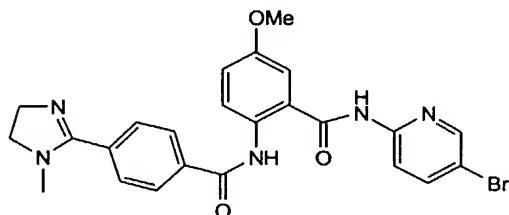


This compound was obtained from 5-methoxy-2-nitrobenzoic acid and 2-amino-5-bromo-pyridine according to the procedure described in Example 259. MS found for  $C_{21}H_{15}BrN_4O_3$  ( $M+H$ )<sup>+</sup>: 451.00, 453.00.

10

Example 273

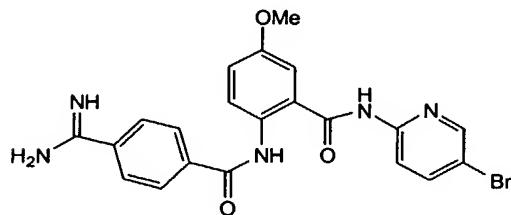
15   **N-(5-bromo(2-pyridyl))(5-methoxy-2-{[4-(1-methyl(2-imidazolin-2-yl)phenyl]carbonylamino}phenyl)carboxamide**



The title compound was obtained according to the procedure described Example 263. MS found for  $C_{24}H_{22}BrN_5O_3$  ( $M+H$ )<sup>+</sup>: 508, 510.

Example 274

**4-(N-{2-[N-(5-bromo(2-pyridyl))carbamoyl]-4-methoxyphenyl}carbamoyl)benzenecarboxamidine**

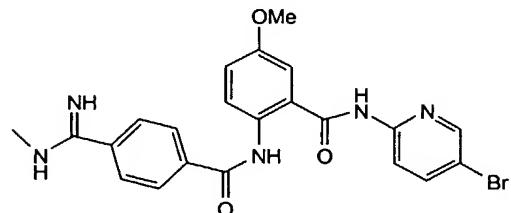


The title compound was obtained according to the procedure described in Example 263. MS found for  $C_{21}H_{18}BrN_5O_3$  ( $M+H$ ) $^+$ : 468.05, 470.00.

10

Example 275

**N-(5-bromo(2-pyridyl))[2-(\{4-imino(methylamino)methyl\}phenyl]carbonylamino)-5-methoxyphenyl]carboxamide**

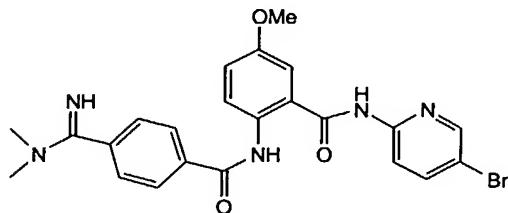


The title compound was obtained according to the procedure described in Example 263. MS found for  $C_{22}H_{20}BrN_5O_3$  ( $M+H$ ) $^+$ : 482, 484.

20

Example 276

5   **[2-({4-[{dimethylamino}iminomethyl]phenyl}carbonylamino)-5-methoxyphenyl]-N-(5-bromo(2-pyridyl))carboxamide**



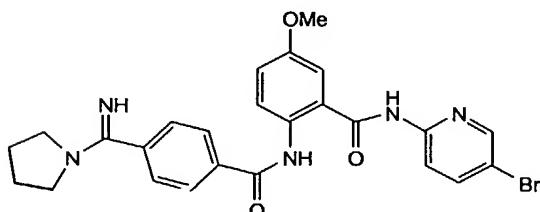
The title compound was obtained according to the procedure described in Example 263. MS found for  $C_{23}H_{22}BrN_5O_3$  ( $M+H$ )<sup>+</sup>: 496.1, 498.1.

10

Example 277

**N-(5-chloro(2-pyridyl))(2-{[4-(iminopyrrolidinylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide**

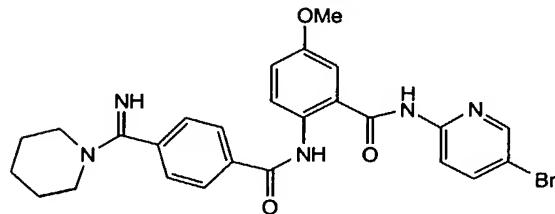
15



The title compound was obtained according to the procedure described in Example 263. MS found for  $C_{25}H_{24}BrN_5O_3$  ( $M+H$ )<sup>+</sup>: 522, 524.

Example 278

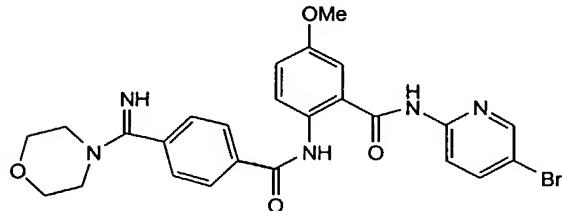
5   **N-( N-(5-bromo(2-pyridyl))(2-{[4-(iminopiperidylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide**



10   The title compound was obtained according to the procedure described in Example  
263. MS found for  $C_{26}H_{26}BrN_5O_3$  ( $M+H$ ) $^+$ : 536.1, 538.1.

Example 279

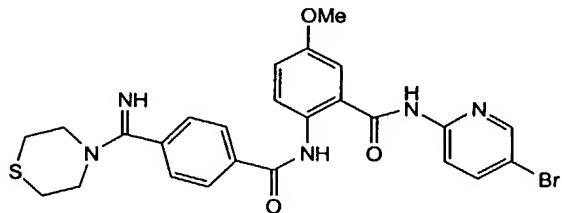
15   **N-(5-bromo(2-pyridyl))(2-{[4-(iminomorpholin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide**



The title compound was obtained according to the procedure described in Example  
263. MS found for  $C_{25}H_{24}BrN_5O_4$  ( $M+H$ ) $^+$ : 538.1, 540.1.

Example 280

5      **N-(5-bromo(2-pyridyl))(2-{{[4-(imino-1,4-thiazaperhydroin-4-ylmethyl)phenyl]carbonylamino}-5-methoxyphenyl)carboxamide**

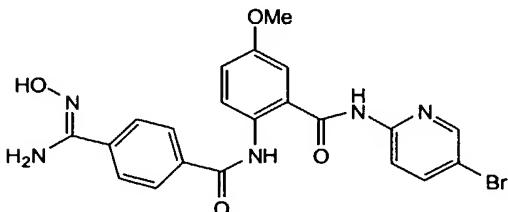


The title compound was obtained according to the procedure described in Example 263. MS found for  $C_{25}H_{24}BrN_5O_3S$  ( $M+H$ ) $^+$ : 554.1, 556.05.

10

Example 281

15      **(2-{{[4-(amino(hydroxyimino)methyl)phenyl]carbonylamino}-5-methoxyphenyl)-N-(5-bromo(2-pyridyl))carboxamide**



The title compound was obtained according to the procedure described in Example 270. MS found for  $C_{21}H_{18}BrN_5O_4$  ( $M+H$ ) $^+$ : 484.1, 486.0.